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NEW APPROACHES TO THE SYNTHESIS OF α -GLUCOPYRANOSIDES

BY

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled, NEW APPROACHES TO THE SYNTHESIS OF α -GLUCOPYRANOSIDES submitted by A. Richard Morgan, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

ABSTRACT

Iodonium and bromonium di-(aromatic heterocyclic amine) perchlorates were prepared by a general method, which involved reaction of dry silver diamine perchlorate complexes with halogens. When the halogen was chlorine, no stable complex was isolated. The iodonium and bromonium di-s-collidine perchlorates reacted with D-glucal triacetate and 2,3,4,6-tetra-O-acetyl- β -D-glucopyranose in a modified Prevost reaction to produce, after deacetylation, β -D-glucopyranosyl 2-deoxy-2-iodo- and bromo- α -D-mannopyranosides, respectively. These disaccharides were hydrogenolysed to 2-deoxydisaccharides. An attempt to prepare an α,α -linked disaccharide led to a correction of the literature regarding the synthesis of 2,3,4,6-tetra-O-acetyl- α -D-glucopyranose. All reported preparations of this compound in fact lead to 1,3,4,6-tetra-O-acetyl- α -D-glucopyranose, which in aqueous solution readily mutarotates, due to 1,2-acetyl migration.

Halonium complexes containing α -picoline and pyridine, which are sterically less hindered than s-collidine, reacted with D-glucal triacetate to form quaternary N-glycosides having the 2-deoxy-2-halogeno- α -D-manno- and β -D-gluco- configurations. These compounds were found to have interesting conformational properties and optical rotatory dispersion curves. In preparing further quaternary N-glycosides for the study of these parameters, it was discovered that bromide ion had a profound effect on the course of the reaction of 2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl bromide with pyridine. An investigation of the mechanism of the re-

action led to the conclusion that the bromide ion catalysed the formation of an intermediate 1,2-acetoxonium ion, which in the presence of pyridine gave rise to an α -nucleoside. When pyridine was replaced by *s*-collidine and an alcohol was added, an orthoacetate was formed by attack of the alcohol on the 1,2-acetoxonium ion. Thus a new route to orthoesters in excellent yield was developed.

In view of the formation of an α -nucleoside from the 1,2-acetoxonium ion in the presence of pyridine, an attempt was made to rearrange 1,2-(alkyl orthoesters) of glucose to α -glucosides on acid catalysis. Of the two diastereoisomeric orthoesters formed, the one with the "endo" alkoxy group would be expected to rearrange to an α -glucoside. Since orthobenzoates and orthopivalates still contained mainly the "exo" isomer in the crude product as evidenced by the n.m.r. spectra and other data, an orthocarbonate was synthesized. However no appreciable yields of α -glucosides could be obtained unless an alcohol was added. Analysis then showed up to 70% yields of α -glucosides. A mechanistic investigation proved that a rearrangement did not take place, but that an ester was eliminated, leaving a free 2-hydroxyl group. That 3,4,6-tri-O-acetyl-1,2-anhydro- α -D-glucopyranose ("Brigl's Anhydride") was an intermediate seemed improbable since its reaction with the alcohols catalysed by *p*-toluenesulphonic acid gave greater amounts of the alkyl β -glucoside triacetate than was obtained from the orthoesters.

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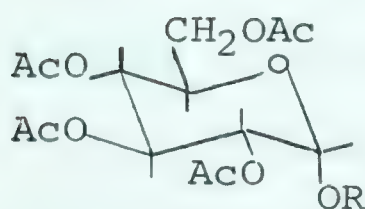
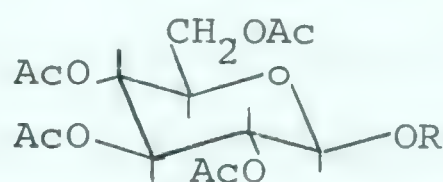
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INTRODUCTION

A. A SHORT HISTORY OF α -GLUCOSIDE SYNTHESIS

The structures shown in Diag. 1 are those of α -D-glucopyranosides and β -D-glucopyranosides. The anomeric carbon is that bearing the acetal function, and it is numbered carbon-1, the other carbon atoms in the chain being numbered successively. The RO-grouping is termed the aglucone. R is bonded to the oxygen through a carbon atom, and may commonly be an alkyl radical,

An α -D-glucopyranosideA β -D-glucopyranoside

Diag. 1

or other sugar in the case of disaccharides.

In the last few years, the discovery of the α -glucosidic linkage in various antibiotics, for example the neomycins, paromomycins and kanamycins (1,2), has stimulated attempts to synthesize α -glucosides and their deoxyamino derivatives. Apart from these practical interests, α -glucosides are of academic interest, having been found in every type of living organism with a diversity of aglucones.

One of the earliest attempts at glucoside synthesis was made as a result of the observation by Hill (3) that the hydrolysis of maltose by the enzyme yeast maltase was retarded by glucose. It was therefore concluded that the enzymatic hydrolysis was a reversible process, and by using the reverse reaction Hill (4) was able to prepare, by the action of yeast maltase on glucose, both maltose and another disaccharide named "revertose". "Revertose" was later shown to be isomaltose (5). Other workers have since applied Hill's general observations and, as may be gauged by recent reviews (6), the field of enzymatic synthesis of glycosides is rapidly growing. Hassid and Doudoroff (6) have reviewed the synthesis of disaccharides with bacterial enzymes. Enzymes are highly specific in their action, although not entirely so. For example, sucrose phosphorylase of Pseudomonas saccharophilia will combine α -D-glucose 1-phosphate with D-fructose to produce sucrose. The D-fructose may be substituted by L-sorbose, D-xyloketose and L-araboketose to produce analogs of sucrose. On the other hand if α -D-galactose 1-phosphate, α -D-mannose 1-phosphate, α -D-xylose 1-phosphate or α -L-glucose 1-phosphate are substituted for α -D-glucose 1-phosphate the enzyme is incapable of synthesizing a disaccharide.

Thus whilst enzymatic synthesis will undoubtedly become ever more important in the synthesis of complex carbohydrates, the difficulty of finding the right enzyme system to produce a specific structure is considerable.

A very general method of producing glycosides is by the acid-catalysed condensation of a sugar with an alcohol or other



sugar. This is known as the Fischer reaction (7). At equilibrium the α -glucosides predominate and may be obtained in about 65% yields from simple alcohols (8). Bishop and Cooper have made an extensive analysis of the pentoses (9), and their conclusions are readily extended to the hexoses. When the reaction is applied to the preparation of disaccharides it is known as the reversion reaction of sugars since, during the hydrolysis of polysaccharides with acid catalysts, the monosaccharides may revert to other di- and oligo-saccharides. For example, Fischer (10) obtained isomaltose on reacting glucose in hydrochloric acid. Disaccharides prepared by this method are obtained in poor yield since condensation can occur at any of the hydroxyl groups. Theoretically eleven pyranosyl-disaccharides may be formed on condensation of glucose. Seven of these were actually isolated from the product formed in the acid-catalysed condensation of glucose (11).

By the use of blocking groups, first practised by Purdie and Irvine (12), a more controlled synthesis is obtained. Thus, condensation of 2,3,4,6-tetra-O-methyl- β -D-glucopyranose in benzene with hydrogen chloride gave a mixture of the octamethyltrehaloses. There was no deliberate control of the stereochemical route of reaction.

The Koenigs-Knorr reaction (13) is widely used in glycoside synthesis, and is more stereospecific. An O-acylated glycosyl halide* and an alcohol are condensed with elimination of hydro-

* The term "acetohalogenosugar" has been used to describe fully O-acetylated glycosyl halides. For reasons of convenience this trivial nomenclature will be used in this thesis provided no ambiguity can arise.

gen halide on catalysis by silver salts. The acetohalogenosugar normally prepared is the α -anomer, since it is the more stable. That an axial halogen at the anomeric center should be thermodynamically favored has been termed the anomeric effect (14,15). Since the Koenigs-Knorr reaction proceeds with Walden inversion, it is therefore a good route to β -glucosides (16). A number of β -acetohalogenosugars have also been prepared but, where there is a 1,2-trans-arrangement as in the β -gluco configuration, they react to give orthoesters under Koenigs-Knorr conditions (17,18).

To avoid neighboring group participation various substituents on carbon-2 have been utilized, some of which are given below.

When Brigl (19) fused β -D-glucopyranose pentaacetate with phosphorous pentachloride, he obtained 3,4,6-tri-O-acetyl-2-O-trichloroacetyl- β -D-glucopyranosyl chloride. The strong inductive effect of the three chlorines reduces the electron density on the carbonyl group to such an extent that neighboring group participation is almost eliminated. Hickinbottom (20) utilized this fact to prepare α -glucosides. Some anomerization of the β -halide to the α -anomer gives rise to the production of β -glucoside, but under optimum conditions a 90% yield of the methyl α -glucoside was obtained from a methanolic solution of the chloride prepared by Brigl in the presence of silver nitrate and pyridine.

The above chloride can be selectively hydrolysed to 3,4,6-tri-O-acetyl- β -D-glucopyranosyl chloride. The hydroxyl group similarly shows little tendency to participate (except in alka-

line solution (21)), and α -glucosides may be obtained under Koenigs-Knorr conditions (20).

Other non-participating groups such as 2-O-nitro (22) have proved successful in α -glucoside synthesis.

In the Zemplen modification of the Koenigs-Knorr reaction, wherein mercuric acetate was used as the condensing agent in place of silver salts, α - and β -glycosides were produced (23). When the alcohol concentration was low, α -glycosides were formed but when it was high, β -glycosides. Lindberg (24) studied the mechanism and proposed that the β -glycoside is in fact formed but at suitable concentrations, mercuric bromide and hydrogen bromide form the complex HHgBr_3 , which catalysed the anomerization of the β -glycoside. Matsuda (25) obtained α -kojibiose octaacetate from the condensation of equimolar portions of 1,3,4,6-tetra-O-acetyl- α -D-glucopyranose and 2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl bromide in the presence of mercuric cyanide in nitromethane. Two other disaccharides, nigerose and laminaribiose were similarly obtained (26). Lehmann and Beck (27) also obtained the retention of configuration of the glycosyl halide with mercuric cyanide in nitromethane. 1,3,4,6-Tetra-O-acetyl- α -D-glucopyranose and tetra-O-acetyl- α -D-galactopyranosyl bromide reacted to give 2-O-(α -D-galactopyranosyl)-D-glucose after deacetylation of the product. A similar reaction with tri-O-acetyl- β -L-arabinosyl bromide (axial bromine) gave rise to 2-O-(β -L-arabinosyl)-D-glucose.

Other variations of the Koenigs-Knorr reaction, such as the fusion of acetohalogenosugars with molten sodium in air,

have been used. Sharp and Stacey (28) obtained trehalose-type disaccharides on fusing 2,3,4,6-tetra-O-acetyl- α -D-galactopyranosyl bromide with sodium in air, (sodium oxide presumably being the active agent, since under nitrogen no reaction was obtained). The disaccharide appeared to have the α,β -configuration.

Hickinbottom (29) first observed the formation of α -glucosides from 3,4,6-tri-O-acetyl-1,2-anhydro- α -D-glucopyranose ("Brigl's anhydride"). Brigl (30) and Hickinbottom (29) had prepared β -glucosides when methanol, ethanol and isopropanol had opened the anhydro ring. Hickinbottom noted that with phenol the phenyl 3,4,6-tri-O-acetyl- α -D-glucopyranoside was formed. On reaction of Brigl's anhydride with 2,3,4,6-tetra-O-acetyl- β -D-glucopyranose, Haworth and Hickinbottom (31) obtained α,β -trehalose heptaacetate. Lemieux extended the reaction to the synthesis of sucrose (32), long a goal of carbohydrate chemists, as well as the naturally occurring α,α -trehalose (33) and maltose (34). The suggested mechanism was that the six-acetoxy group participated with a double Walden inversion at the anomeric center. Lloyd and Roberts (35) recently postulated six-acetoxy participation to account for an 83% yield of the α -glucoside when 3,4,6-tri-O-acetyl-2-deoxy-2-N-(2,4-dinitroaniline)- α -D-glucopyranosyl bromide is reacted with excess ethanol in the presence of pyridine. When silver carbonate is used the β -glucoside is predominantly formed.

The anomerization of β -glycosides to their α -anomers is achieved with acid catalysts. Pacsu (36) anomerized methyl β -D-glucopyranoside tetraacetate in chloroform with stannic chloride

and titanium tetrachloride. The reaction was extended by Lindberg to disaccharides (37,38). The octaacetate of β -melibiose, (6-O- α -D-galactopyranosyl D-glucose), was prepared by the anomerization of the β -anomer in chloroform with titanium tetrachloride. Similarly β -isomaltose octaacetate was obtained from gentiobiose octaacetate in 46% yield. The mechanism was studied by Lindberg (39) and he suggests that the pyranose ring is broken open to form a zwitter ion which collapses back to the α -anomer. Lemieux and Shyluk (40) prefer the mechanism whereby the acid catalyst attacks the aglucone group. This leads to a fairly stable ion-pair structure which can collapse to the α -glucoside instead of leading to separated ions.

This brief history of the development of α -glucoside synthesis serves to indicate the complex nature of the problem, and how stereochemical, mechanistic and thermodynamic considerations must be considered in any new approach.

B. A SURVEY OF THE LITERATURE PERTINENT TO THE PRESENT WORK

1. 2-Deoxy-2-halogenoglycosides

Lemieux and Levine (41) reinvestigated the products of the Prevost reaction (42) on D-glucal triacetate, and showed that the conclusions of Stanek and Schwarz (43) were erroneous. Lemieux and Levine proved that the reaction of D-glucal triacetate with iodine and silver benzoate in dry benzene formed an approximately equimolar mixture of the products of trans-addition to the double bond, (1-O-benzoyl-2-iodo-2-deoxy- β -D-glucopyranose triacetate

and the stereoisomer with the α -D-manno-configuration). In a later paper (44) they extended the reaction to the preparation of glycosides. The methyl, cyclohexyl, and t-butyl 2-deoxy-2-iodo- α -D-manno- and β -D-glucopyranoside triacetates were formed nearly quantitatively when equimolar amounts of the corresponding alcohol, iodine, D-glucal triacetate, silver perchlorate and s-collidine reacted in dry benzene. The larger the alcoholic grouping, the more of the α -manno-stereoisomer was formed (85% for t-butyl), and since the iodine is readily hydrogenolysed with palladium on charcoal as the catalyst, this provides an excellent route to 2-deoxy- α -D-glucopyranosides.

Further research by Lemieux and Fraser-Reid (45) led to the extension of the reaction to bromo derivatives. Bromination of D-glucal triacetate produced the 2-bromo-2-deoxy-D-glycopyranosyl bromides with the α -manno- and α -gluco-configurations. Methoxylation in the presence of silver carbonate proceeded with Walden inversion at the anomeric center to give the methyl β -D-glycosides. Direct halogenomethoxylation was obtained when D-glucal triacetate reacted with bromine, chlorine or iodine in methanol containing silver acetate. The methyl 2-deoxy-2-halogenoglycopyranosides with the α -manno- and β -gluco-configurations were formed in 60-65% and 35-40% yields respectively.

2. Preparations of Orthoesters

Pascu has given a good review of orthoesters up to 1945 (17). At that time it was recognized that 1,2-trans-acetohalogenosugars under Koenigs-Knorr conditions gave rise to orthoacetates and in



fact orthoacetate formation was used as evidence in the assignment of the anomeric configuration (46). α -Acetobromoglucose is a 1,2-cis-acetohalogenosugar, and consequently straight S_N^2 attack with Walden inversion at the anomeric center to give β -glucosides is found under Koenigs-Knorr conditions. On the other hand if the 1,2-trans-acetohalogenosugar, β -D-glucopyranosyl chloride tetraacetate, is employed, orthoesters can be prepared in good yield (47). Also all cases where the 2-acetoxy group is axial and trans to the anomeric halogen, such as compounds with the manno- and lyxo- configurations, can give rise to orthoesters. For example, Levene and Wolfrom (48) reacted syrupy α -D-lyxopyranosyl bromide triacetate with methanol in quinoline to obtain the 1,2-(methyl orthoacetate).

Evidence that orthoesters could be obtained from 1,2-cis-acetohalogenosugars was obtained by Helferich, Doppstadt and Gottschlich (49). They attempted to synthesize glycosides in a homogeneous medium by the reaction of α -acetobromoglucose with an alcohol in *s*-collidine. They unexpectedly obtained an over 50% yield of the 1,2-(isopropyl orthoacetate) when isopropanol was the alcohol. When methanol was used instead, a moderate yield of the methyl β -D-glucopyranoside tetraacetate was isolated. On the other hand when Helferich and Weis (50) treated α -benzobromoglucose with methanol and *s*-collidine in nitromethane, the 1,2-(methyl orthobenzoate) was obtained in 80% yield as a syrup. Other cases are also recorded of orthoesters being isolated from α -acetobromoglucose. Weygand and Ziemann (51) treated α -acetobromoglucose with ethanol (large excess) and

pyridine (excess) in ether and obtained the 1,2-(ethyl orthoacetate) in about 50% yield. An interesting product related to orthoesters was shown to be formed when α -acetobromoglucose reacted with silver cyanide in boiling xylene (52). Besides 2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl cyanide, 3,4,6-tri-O-acetyl-1,2-O-(1-cyanoethylidene)- α -D-glucopyranose was isolated.

A new asymmetric carbon atom is formed when orthoesters of sugars are prepared and diastereoisomers are expected. These were first isolated when two disaccharide orthoesters were prepared from 1,2,3,4-tetra-O-acetyl- β -D-glucopyranose and α -acetobromomannose in the presence of silver oxide and Drierite in alcohol-free chloroform (53). These were called d- and l-(β -D-glucose-1,2,3,4-tetraacetate-D-mannose-3',4',6'-triacetate 6,1',2'-orthoacetate). More recently Perlin (54) isolated the two crystalline diastereoisomers of β -D-mannose 1,2-(benzyl orthoacetate) and by the use of n.m.r. spectroscopy confirmed the presence of diastereoisomers in all the orthoacetate preparations considered.

3. Reactions of Sugar 1,2-(Alkyl Orthoesters)

Only those aspects of the reactions of orthoesters pertinent to the present thesis will be considered.

It is well known that orthoesters are extremely sensitive to acid hydrolysis but relatively resistant to alkaline hydrolysis. Lemieux and Ciperia (47) in their studies of α -D-glucopyranose 1,2-(ethyl orthoacetate) triacetate, conclude that it reacts quantitatively with trace amounts of water in acetic acid. The

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orthoester structure readily reverts to the cyclic acetoxonium ion in acid solution, which reacts with water to give the transient acid orthoacetate. The so-called acid orthoacetate can then rearrange to various products.

In keeping with the extremely facile production of the acetoxonium ion is the observation that 1,4,6-tri-O-benzoyl-2,3-(benzyl orthobenzoate)- β -D-fructofuranose is converted into the corresponding ethyl orthobenzoate derivative in ethanol with a trace of acid (55).

Although orthoesters are very labile compounds, they have not been studied very extensively as synthetic intermediates. This is probably due to the complexity of their reactions, apart from the lack of their general availability. Perlin (56) treated β -D-mannopyranose 1,2-(methyl orthoacetate)-3,4,6-tri-O-acetate with hydrogen chloride in methanol and obtained mainly 3,4,6-tri-O-acetyl-D-mannose and some 2,4,6-tri-O-acetyl-D-mannose involving a novel acetyl migration from the 3- to the 2-position. But when Perlin used α -D-glucopyranose 1,2-(ethyl orthoacetate)-3,4,6-tri-O-acetate in place of the mannose 1,2-(orthoacetate) he obtained 3,4,6-tri-O-acetyl-D-glucose and methyl 3,4,6-tri-O-acetyl- β -D-glucopyranoside.

Russian workers (57) have reported the synthesis of β -glucosides from α -D-glucopyranose 1,2-(methyl orthoacetate)-3,4,6-triacetate. For example when the orthoacetate was reacted with cholesterol in boiling nitromethane in the presence of 0.001 moles HgBr_2 and 0.00075 moles of p-toluenesulphonic acid per mole of the orthoacetate, there was isolated cholesteryl 2,3,4,6-

tetra-O-acetyl- β -D-glucopyranoside (15%) and α -D-glucopyranose 1,2-(cholesteryl orthoacetate)-3,4,6-tri-O-acetate (26%). By varying the conditions the reaction could be made to yield either the β -glucoside or the orthoacetate as the main product.

Acetylated orthoesters react with hydrogen chloride and titanium tetrachloride in chloroform (53) to give acetochlorosugars.

EXPERIMENTAL

All melting points were taken on a heating stage and are uncorrected.

All nuclear magnetic resonance (n.m.r.) spectra were determined, unless otherwise stated, in chloroform with a Varian A60 spectrometer and the chemical shifts are reports in tau (τ) values, with tetramethylsilane (TMS) as internal standard.

Paper chromatograms of acetylated derivatives were done on Whatman No. 1 paper impregnated with dimethylsulphoxide (DMSO) and with Skellysolve B as the irrigant (58). The acetates were detected by spraying first with a mixture of equal volumes of 1.1 N potassium hydroxide in methanol and 1 N hydroxylamine hydrochloride in methanol. The precipitate of potassium chloride formed in the preparation of the spray reagent need not be removed by filtration. After drying the paper at 120° for five minutes, spraying with ferric nitrate solution (20 g of ferric nitrate monohydrate in 300 ml water and 200 ml glacial acetic acid) developed the chromatogram as purple spots (59).

Deacetylated material was chromatographed on Whatman No. 1 paper and developed with the lighter phase of n-butanol, ethanol and water mixture (5:1:4) (60). The components were detected by dipping the paper first in a solution of silver nitrate prepared by adding 1 ml of saturated aqueous solution of silver nitrate to 200 ml of acetone and then adding just sufficient water to redissolve the precipitate. The paper was then sprayed with a 0.5 N solution of sodium hydroxide prepared by dissolving 5 g sodium

hydroxide in 7.5 ml water and diluting to 250 ml with ethanol (61). Papers to be preserved were washed with ammonia after the spots had developed to their maximum intensity. Periodate-permanganate (62), p-anisidine hydrochloride (63) and aniline hydrogen phthalate (64) sprays were also used. R_G numbers refer to the R_f values relative to that of glucose.

Chloroform, where used in preparative procedures, was purified by passing down an activated alumina column. A column 1.9 cm x 28 cm gave 400 ml chloroform with no trace of hydroxyl absorption in the infrared. Methylene chloride was similarly purified.

A. COMPLEXES OF s-COLLIDINE,* α -PICOLINE AND PYRIDINE

It is important to realize that perchlorates are potentially powerful explosives. Although none of the preparations described below caused trouble, the compounds detonated on strong heating. Due precautions must be taken (65).

1. Silver Perchlorate Complexes

a. Silver Di-s-collidine Perchlorate (1)

s-Collidine, 20 ml, was added with vigorous stirring to a solution of silver nitrate, 9 g (53 mmoles), and sodium perchlorate, 11 g, in 100 ml water to give a white curdy precipitate. After washing repeatedly with water, the product (1) was washed with ethanol and ether and finally dried under vacuum over phosphorous pentoxide. The yield was 24 g (100%).

* 2,4,6-Trimethylpyridine.

b. Silver Di- α -picoline Perchlorate (2)

α -Picoline, 10 ml, and sodium perchlorate, 12.2 g (100 mmoles), in 125 ml water were added with stirring to silver nitrate, 5.7 g (35.5 mmoles), in 25 ml water. The precipitate, 13.1 g (100% yield), was washed with water and dried under vacuum over phosphorous pentoxide.

c. Silver Dipyridine Perchlorate (3)

Pyridine, 43 ml, and sodium perchlorate, 40 g, in 200 ml water were added to silver nitrate, 32.7 g (192 mmoles), in 120 ml water with stirring. The heavy white precipitate was washed with water, air dried, dissolved in 100 ml chloroform and 20 ml pyridine. The fine precipitate obtained on adding ether was dried in vacuo. The yield was 70 g (99%).

2. Iodonium Perchlorate Complexes

It is important in the preparation of all halonium ions to make sure the conditions are anhydrous. Otherwise, the halogen tends to be re-liberated.

a. Iodonium Di-s-collidine Perchlorate (4)

Powdered iodine, 20.2 g (79.5 mmoles), was added to a suspension of the perchlorate (1), 35.7 g (79.5 mmoles), in about 200 ml of pure chloroform and 5 ml of s-collidine. After shaking for 15 minutes, the yellow precipitate of silver iodide was removed by filtration through a bed of Celite and compound 4 crystallized directly from the filtrate on standing in the cold. The mother liquors gave further fine white crystals on the addition of ether. The combined crystals were dried under high vacuum and analyzed for positive iodine as follows.

Compound 4, 0.4647 g, was partially dissolved in 10 ml chloroform and 2 g of potassium iodide were added. Titration with 0.1 M sodium thiosulphate required 19.4 ml. Excess hydrochloric acid, to neutralize the s-collidine, was added before the end point which was determined with starch indicator. Thus, 97.5% of the theoretical iodine was liberated based on the formula $(C_8H_{11}N)_2IClO_4$.

b. Iodonium Di- α -picoline Perchlorate (5)

Solutions of iodine, 25.4 g (100 mmoles), and perchlorate, 2, 39 g (99 mmoles), in dimethylformamide (dried over potassium hydroxide) were mixed and 5 ml of α -picoline were added. Immediately, a yellow precipitate of silver iodide was observed and, after being briefly shaken, the solution was rapidly filtered through Celite. Crystals of the iodonium salt (5) were already forming. The Celite was washed with a little dimethylformamide. Ether was added to the filtrate. The precipitate, 21.2 g (51.5% yield), was titrated for iodonium ion as indicated for the iodonium salt (4). A 0.2873 g sample required 13.9 ml of 0.1 M thiosulphate. The calculated volume for $(C_6H_7N)_2IClO_4$ is 13.95 ml.

The n.m.r. spectrum in dimethylsulphoxide had the signals for the four aromatic protons to rather low field, 0.8-2.7 τ , as compared with those, 1.3-3.0 τ , for α -picoline in the same solvent.

c. Iodonium Dipyridine Perchlorate (6)

Finely powdered iodine, 27.8 g (109 mmoles), was added to the perchlorate, 2, 46.5 g (118 mmoles), dissolved in dry pyridine. The silver iodide was removed by filtration with the aid of Celite and washed with chloroform. The filtrate gave 31.4 g

of a white crystalline powder. A further 9.2 g was obtained on adding ether. The total yield, based on iodine, was 90%. The positive iodine content was 97.5% of the theoretical for $(C_5H_5N)_2IClO_4$.

3. Bromonium Complexes

a. Bromonium Di-s-collidine Perchlorate (7)

Silver di-s-collidine perchlorate(1), 13.47 g (30 mmoles), was suspended in 150 ml pure chloroform and 1 ml s-collidine, and 1.65 ml bromine (30 mmoles) was added. Silver bromide was rapidly precipitated and was collected by filtration on Celite. The clear faint-yellow filtrate gave a fine, white crystalline precipitate on the addition of ether. A 70% yield was obtained of a product which, on analysis contained 93% of the positive bromine expected for $(C_8H_{11}N)_2BrClO_4$. The n.m.r. spectrum (see Fig. 1) in methylene chloride is that expected for complexed s-collidine. The intensities of the signals at 2.72, 7.15 and 7.57 τ were 2:6:3, respectively. s-Collidine in methylene chloride gave signals of corresponding relative intensities at higher field 3.22, 7.59 and 7.77 τ , respectively. The melting point was ill-defined but a clear liquid was obtained at 230°.

b. Bromonium Di- α -picoline Perchlorate (8)

Bromine, 5.3 ml, was added to a vigorously stirred solution of 37 g (94 mmoles) of silver di- α -picoline perchlorate(2) dissolved in a minimum of dimethylformamide and containing 5 ml of α -picoline. The precipitated salts were removed by filtration and, on adding ether to the filtrate, the product crystallized rapidly. Since the product reacted with the solvents, it was

isolated as rapidly as possible. Iodometric titration showed a positive bromine content 94.5% of the value expected for $(C_6H_7N)_2BrClO_4$.

c. Bromonium Dipyridine Perchlorate (9)

The procedure described for the preparation of iodonium dipyridine perchlorate (6), was followed except that bromine was substituted for the iodine. The product was found to contain 99% of the positive bromine expected for $(C_5H_5N)_2BrClO_4$.

4. The Chloronium Cation

a. The Reaction of Silver Di-s-collidine Perchlorate with Chlorine

The silver complex (1), 10 g, was suspended as a fine powder by stirring in chloroform and chlorine gas was bubbled through the suspension. After 15 minutes, the white suspension had coagulated and an exothermic reaction had taken place. The filtrate, after removal of insoluble salts on a Celite bed, yielded a crystalline precipitate on adding Skellysolve B. This was shown to be s-collidinium perchlorate (Section B.1.a.). The filtrate was evaporated under reduced pressure with cooling of the mixture and a further crop of crystals was obtained. These crystals were transformed to an oil on warming to room temperature. Gas-liquid partition chromatography of this oil (silicone oil column, programmed for 80° to 200° at 11° per minute) showed one major peak with a longer retention time than s-collidine and other minor products. The oil distilled at about 198-205° and the distillate had the n.m.r. spectrum shown in Fig. 2.

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b. The Reaction of Silver Dipyridine Perchlorate with Chlorine

The silver complex (3), 10 g, as a suspension in 125 ml of chloroform, reacted to give a bright yellow color when chlorine was first bubbled through the solution, but the yellow color gradually disappeared. The filtrate from the reaction slowly yielded a heavier liquid phase when Skellysolve B was added. On standing overnight at 0°, crystals were not deposited.

B. PREPARATION OF 2-DEOXY-2-HALOGENOGLYCOSIDES

1. 2-Deoxy-2-iodo-glycosides

a. Methyl 3,4,6-tri-O-acetyl-2-deoxy-2-iodo- α -D-mannopyranoside (10) and the Corresponding β -Glucoside (11)

Anhydrous methanol, 0.12 ml (2.8 mmoles), and 1.3 g of iodonium complex (4) (titration gave 86% of the theoretical iodine) were added to D-glucal triacetate, 0.755 g (2.78 mmoles), dissolved in 15 ml of pure chloroform. A homogeneous faint-yellow solution was obtained from which, almost immediately, s-collidinium perchlorate separated. The precipitate was characterized through its solubility in water, the liberation of s-collidine on adding potassium hydroxide solution, and the precipitation of potassium perchlorate when a concentrated aqueous solution was mixed with concentrated potassium iodide solution. The mixture was filtered after a 20 minute reaction time and the filtrate washed first with water, then with 2 N sulphuric acid and finally with water, and, after drying by filtration through chloroform-wetted paper was evaporated at high vacuum to a syrup,

1.115 g (93.3% yield of 2-deoxy-2-iodoglycosides). The n.m.r. spectrum, Fig. 3, is almost identical to that obtained by Lemieux and Levine (44) except that integration of the methoxyl peaks indicated 82% of the α -manno and 18% of the β -gluco configurations. The Lassaigne's sodium fusion test confirmed the presence of iodine in the molecule.

b. β -D-Glucopyranosyl 2-Deoxy-2-iodo- α -D-mannopyranoside (12)

The iodonium complex (4), 12.17 g (23.7 mmoles of positive iodine as determined by titration which gave 91% of the theoretical value), was added to D-glucal triacetate, 6.45 g (23.7 mmoles), and 8.25 g (23.7 mmoles) of 2,3,4,6-tetra-O-acetyl- β -D-glucopyranose dissolved in 50 ml of pure chloroform. As the iodonium salt dissolved on stirring the mixture s-collidinium perchlorate was precipitated. After 20 minutes, a sample of the solution was added to aqueous potassium iodide solution containing soluble starch. A strong blue color developed. After six hours, the brownish solution was filtered to remove the s-collidinium perchlorate which had precipitated (4.62 g, theoretical yield 5.23 g but it is appreciably soluble in chloroform). The filtrate was washed with 0.1 M sodium thiosulphate, 60 ml, to give a light-brown chloroform layer. Iodine was liberated on standing. On passing the chloroform layer down a silicic acid column (1.8 cm x 19.5 cm), a band with the violet color of iodine ran ahead and was followed by a brown band from which a syrup was isolated. The syrup was deacetylated by allowing a solution in methanol containing 2 ml of triethylamine and water added to turbidity, to stand overnight at room temperature. A paper chromatogram of

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of the deacetylated syrup showed a spot with $R_G=1.19$ and a trace of glucose with the aniline hydrogen phthalate spray reagent. The compound, 2.84 g, crystallized from water (on seeding with crystals obtained in an earlier experiment from a chromatographic purification on a Celite column using n-butanol-water (66)). A further 0.5 g was obtained by crystallization of the residual syrup from methanol. The total yield was about 33%. Recrystallization from water gave material of m.p. 158° (dec.) and $[\alpha]_D + 27.6^\circ$ (c, 1 in water); $\lambda_{\max}^{\text{MeOH}}$ 255 $m\mu$ ($\epsilon 470$), typical of the carbon-iodine bond. The n.m.r. spectrum is shown in Figs. 4 and 5. Anal. Calcd. for $C_{12}H_{21}O_{10}I \cdot H_2O$: C, 30.65; H, 4.93; I, 27.00. Found: C, 30.19; H, 5.00; I, 27.94. Since the crystals obtained from methanol melted with decomposition at $164-5^\circ$ and $[\alpha]_D + 36.5^\circ$ (c, 1.1 in water), and in view of the elemental analysis, the product crystallized from water was likely a monohydrate.

Further elution of the silicic acid column gave 0.6 g of syrup that, on deactylation, gave spots corresponding to glucose and glucal on paper chromatograms.

c. 2,3,4,6-Tetra-O-acetyl- β -D-glucopyranosyl 2-Deoxy-3,4,6-tri-O-acetyl- α -D-glucopyranoside (13).

The above described compound (12), 0.163 g (0.36 mmoles), dissolved in 2.5 ml water and 0.3 ml triethylamine, was hydrogenolyzed with a 10% palladium-on-charcoal catalyst. After stirring for 2 hours under hydrogen at slightly above atmospheric pressure, the theoretical quantity of hydrogen was taken up. The catalyst was removed by filtration using Celite. Silver carbonate, 10 mmoles, was added to the filtrate to precipitate the iodide ion. Filtra-

tion followed by passage of hydrogen sulphide to remove traces of silver salts and evaporation of the clarified solution left 0.135 g of brown residue which was acetylated in 5 ml pyridine and 5 ml acetic anhydride. After standing overnight, the solvents were evaporated to leave 0.207 g of a semi-crystalline syrup. Two recrystallizations from ethanol gave fine crystals, m.p. 163.5° and $[\alpha]_D + 66.5^{\circ}$ (c, 0.8 in chloroform). Anal. Calcd. for $C_{26}H_{36}O_{17}$: C, 50.25; H, 5.80. Found: C, 50.25; H, 5.79. The n.m.r. spectrum is shown in Fig. 6. The compound was deacetylated with sodium methoxide in methanol to give a fine, white amorphous powder, $R_G = 0.43$, with the n.m.r. spectrum shown in Fig. 7. A 0.05 g sample of the deacetylated product was dissolved in 5 ml of 0.2 N hydrochloric acid. The observed rotation of 0.65° after 0.5 hours fell to 0.55° after one day. The reaction was also followed chromatographically and after one day essentially all the starting material, $R_G = 0.43$, had hydrolysed to glucose and 2-deoxyglucose as seen by direct comparison with authentic samples on a paper chromatogram.

2. 2-Bromo-2-deoxyglycosides

a. Methyl 3,4,6-Tri-O-acetyl-2-bromo-2-deoxy- α -D-mannopyranoside (14) and the Corresponding β -Glucoside (15)

The bromonium complex (7), 0.965 g (2.12 mmoles of positive bromine as determined by titration), was added to D-glucal triacetate, 0.576 g (2.12 mmoles), and 0.2 ml methanol (4.9 mmoles) in 5 ml pure chloroform. The reaction was exothermic and a rapid precipitation of s-collidinium perchlorate was obtained. After

stirring for ten minutes, the solution was washed with dilute hydrochloric acid containing potassium iodide. Iodine was liberated but 6 ml of 0.1 M thiosulphate solution rendered both phases colorless. The chloroform layer was then washed with sodium bicarbonate, filtered and evaporated overnight in a high vacuum. The residue, 0.818 g (quantitative yield) of a light yellow syrup, gave the n.m.r. spectrum shown in Fig. 8.

b. β -D-Glucopyranosyl 2-Bromo-2-deoxy- α -D-mannopyranoside (16)

The bromonium complex (7), 13.5 g (27.3 mmoles of bromonium ion by titration), was added to D-glucal triacetate, 7.17 g (26.4 mmoles), and 2,3,4,6-tetra-O-acetyl- β -D-glucopyranose, 9.17 g (26.4 mmoles), in chloroform. There resulted an exothermic reaction with precipitation of s-collidinium perchlorate. After five minutes a sample did not liberate iodine when shaken with potassium iodide solution. The reaction mixture was cooled to 0° and about 6 g (27 mmoles) of s-collidinium perchlorate was obtained on filtration. The chloroform filtrate was washed with dilute acid and then sodium bicarbonate.

Evaporation left a syrup which was dissolved in methanol containing 6.5 ml of triethylamine, and water was added to turbidity. The solution turned green and, on standing overnight, became purple. The deacetylated syrup very slowly deposited crystals from methanol, 3.5 g after a month (33% yield). Recrystallization from methanol-water mixture gave material which carbonized around 180°, $[\alpha]_D + 39.4^\circ$ (c, 1 in water), n.m.r. spectra shown in Figs. 9 and 10. Anal. Calcd. for $C_{12}H_{21}O_{10}Br$: C, 35.56; H, 5.32. Found: C, 35.46; H, 5.32.

Recrystallization from water gave crystals which, after drying to constant weight, decomposed around 180° with $[\alpha]_D + 34.6^{\circ}$ (c, 1 in water). Since the R_G value was 0.95, the compound was difficult to distinguish from glucose in the chromatogram of the crude deacetylated syrup.

The compound was hydrogenolysed for two days under the same conditions as described above for compound 12 using palladium-on-charcoal catalyst. The syrup obtained from the reaction was acetylated and worked up exactly as described for the preparation of the deoxy-glycoside 13. The melting point, 163° , was not depressed on admixture with 13.

3. Attempted Preparation of an α,α -Linked Disaccharide

a. 1,3,4,6-Tetra-O-acetyl- α -D-glucopyranose (17)

When essentially the directions of Lemieux and Brice (67), were followed to prepare 2,3,4,6-tetra-O-acetyl- α -D-glucopyranose, the 1,3,4,6-tetraacetate was prepared in 40% yield. 2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl chloride, 36.6 g (100 mmoles), was dissolved in about 100 ml of glacial acetic acid, and 2 ml of water (110 mmoles) and silver acetate 20 g (120 mmoles) were added. The mixture was shaken vigorously for 2 minutes and then frozen in a dry-ice and acetone mixture. The volatile components were removed in vacuo. The residue was finally warmed to 80° in vacuo to remove the last traces of acetic acid. The residue was extracted 5 times with ether and the silver salts were removed on Celite. To the ether filtrate was added Skellysolve B just to the point of turbidity. The crystalline precipitate,

10.5 g (30% yield), m.p. 90-95° had the n.m.r. spectrum expected for the pure 1,3,4,6-tetraacetate. The n.m.r. spectrum of the syrup, 18 g, from the filtrate indicated a further 10.5 g, making a total yield of 60%. When 95% acetic acid was used in place of glacial acetic acid for the preparation, a 40% yield of crystalline material was obtained. Recrystallization from ether-Skellysolve B gave material of m.p. 110-111° $[\alpha]_D + 149^\circ$ (c, 1 in chloroform), n.m.r. spectrum shown in Fig. 11.

1,3,4,6-tetra-O-acetyl- α -D-glucopyranose did not mutarotate in dry pyridine but did in water. The mutarotation in water was followed polarimetrically to constant rotation. The plot of $\log (\alpha - \alpha_\infty) / (\alpha_0 - \alpha_\infty)$ against the time, gave a straight line with slope $1.63 \times 10^{-2} \text{ min.}^{-1}$. The final rotation corresponded to $[\alpha]_D + 71^\circ$ (c, 1.8 in water). The mutarotation of 2,3,4,6-tetra-O-acetyl- β -D-glucopyranose had at the equilibrium point $[\alpha]_D + 71^\circ$ (c, 1.5 in water), with an identical n.m.r. spectrum. The rotation is approximately that expected for a 50/50 mixture of α - and β -glucose tetraacetates.

When the syrup is dissolved in pyridine further mutarotation occurs, and the n.m.r. spectrum in pyridine, Fig. 12, indicates that 77% of the mixture is 2,3,4,6-tetra-O-acetyl- α -D-glucopyranose, based on the integrated values of the anomeric and carbon-3 protons, which are to lower field than any for the β -glucoside tetraacetate. This was confirmed by acetylation and benzylation.

(i) 2,3,4,6-tetra-O-acetyl- β -D-glucopyranose, 0.4 g (1.15 mmoles), was left to mutarotate in pyridine, 1 ml, for 3 days. To this solution was added 0.2 ml of acetic anhydride (2.13 mmoles), and

the mixture was left overnight. On evaporation a residual syrup was obtained which readily crystallized from ethanol. The material had a melting point of 112° which on admixture did not depress the melting point of authentic α -D-glucopyranose pentaacetate.

(ii) Using benzoyl chloride in place of acetic anhydride, an immediate precipitate was observed. After two hours the mixture was poured into a saturated solution of sodium bicarbonate and shaken until no further carbon dioxide was evolved. The oil which separated was extracted with chloroform and the chloroform extract was washed with 2 N sulphuric acid, aqueous sodium bicarbonate, and finally purified on a small silicic acid column to remove any hydroxylated impurities. The chloroform eluate gave an 82% yield of syrup with $[\alpha]_D + 81.6^{\circ}$ (c, 1.2 in chloroform). The syrup crystallized from ethanol-Skellysolve B, m.p. 59.5° , although traces of crystalline material were noted in polarized light disappearing at 110° . The literature values for the properties of 2,3,4,6-tetra-O-acetyl-1-O-benzoyl- α - and β -D-glucopyranose are respectively m.p. $60-63^{\circ}$, $[\alpha]_D^{15} + 113.5^{\circ}$ (c, 3 in chloroform) and m.p. 143° $[\alpha]_D^{20} - 28.1^{\circ}$ (c, 3 in chloroform). The rotation of the syrup corresponds to 79% of the α -anomer, if the above compounds were the only products, and this is in excellent agreement with the interpretation of the n.m.r. spectrum of the mutarotated mixture, Fig. 12.

b. Glycoside Formation Utilizing Syrupy 2,3,4,6-Tetra-O-acetyl- α -D-glucopyranose

D-Glucal triacetate, 1.475 g (5.42 mmoles), and the syrupy

mixture of 2,3,4,6-tetra-O-acetyl- α - and β -D-glycopyranoses from pyridine, 1.87 g (5.37 mmoles), were dissolved in 15 ml of chloroform. The iodonium complex (4), 2.735 g (5.4 mmoles by titration) was added, and, as it dissolved, s-collidinium perchlorate crystallized out of solution. Some decomposition took place and the solution turned a reddy-brown color. After 1.25 hours, salts were removed by filtration, and the filtrate was washed with dilute sulphuric acid containing potassium iodide, thiosulphate solution and finally water. About 20 ml of 0.1 M thiosulphate solution was required to reduce the iodine liberated. The chloroform layer was evaporated to 3.94 g of a syrup which was deacetylated in 100 ml of methanol saturated with ammonia. After one day, on partial removal of solvents, crystals were obtained, 0.56 g, with m.p. 153-155° (dec.). The filtrate was evaporated to a syrup which was chromatographed on 100 g of Celite [Section E.1.c.(ii)]. After the first 900 ml of eluate, 25 ml fractions were collected. Fractions 20-36 yielded 0.307 g of crystals from methanol, m.p. 164-165° (dec.), $[\alpha]_D + 36.5^\circ$ (c, 1.1 in water), and a further 0.166 g from the mother liquors, m.p. 160-169° (dec.).

Reduction of the latter fraction with palladium-on-charcoal as the catalyst in the same manner as described for 12 followed by acetylation yielded material of m.p. 162-163°, $[\alpha]_D + 66.5$ (c, 0.8 in chloroform), which on admixture with the β -D-glucopyranosyl 2-deoxy- α -D-glucopyranoside heptaacetate (13) did not depress its melting point. Paper chromatograms of all three crystalline fractions gave one spot with the same R_G as 12 and their n.m.r. spectra in deuterium oxide were identical, and the

same as that of 12. Therefore the total yield of 12 from the reaction was 39%.

C. PREPARATION OF QUATERNARY N-GLYCOSIDES

1. N-2-Deoxy-2-halogenoglycosides

a. N-(3,4,6-Tri-O-acetyl-2-deoxy-2-iodo- β -D-glucopyranosyl)-pyridinium Perchlorate (18) and the Corresponding α -D-Manno-Stereoisomer (19)

D-Glucal triacetate, 22.2 g (81.7 mmoles), and the iodonium complex (6), 31.4 g (81.7 mmoles), reacted rapidly in 200 ml of chloroform. As the latter dissolved a fine precipitate of the pyridinium glucoside (18) appeared. The reaction mixture was shaken for one hour and compound (18) was isolated by filtration. Fine, needle-like crystals of the pyridinium mannoside (19) were obtained from the chloroform filtrate on standing at 0°.

Compound 18, 33 g (70% yield), was recrystallized from methanol to constant physical properties, m.p. 163-4°, $[\alpha]_D + 109.8^\circ$ (c, 1.1 in methanol), $[\alpha]_D + 133^\circ$ (c, 0.4 in acetone), $\lambda_{\text{max}}^{\text{MeOH}} 260 \text{ m}\mu$ ($\epsilon 4,760$), the n.m.r. spectrum given in Fig. 13 and the o.r.d. data listed in Table I. Anal. Calcd. for $\text{C}_{17}\text{H}_{21}\text{O}_{11}\text{NICl}$: C, 35.34; H, 3.66; N, 2.43; I, 22.0. Found: C, 35.55; H, 3.56; N, 2.59; I, 21.1.

The iodine was determined by digesting 0.578 g (1 mmole), in one molar sodium hydroxide on a steam bath. After acidification with hydrochloric acid, the iodide was oxidized to iodine with 0.1 ml of bromine. The excess bromine was removed by gentle boiling and the last traces by adding phenol. The amount of iodine liber-

ated was determined by titration with standard sodium thiosulphate solution.

Recrystallization of the crude mannoside (19), m.p. 97-102°, 14 g (30% yield), from chloroform was accomplished with difficulty as there was a tendency to obtain an oil, but seeding gave crystals, m.p. 103-4°, $[\alpha]_D - 22.6^\circ$ (c, 1 in methanol), $[\alpha]_D - 15.5^\circ$ (c, 2 in acetone), $\lambda_{\text{max}}^{\text{MeOH}} 258 \text{ m}\mu$ ($\epsilon 4,850$), the n.m.r. spectrum given in Fig. 14, and the o.r.d. data listed in Table I. An iodine analysis of 19 analogous to that for 18 gave 91% of the theoretical iodine content. When pure pyridinium mannoside (19) was dissolved in pyridine, crystals of the isomeric pyridinium glucoside (18) were obtained after one week in about 80% yield. The melting point, mixed melting point and the n.m.r. spectrum were identical with those of 18.

The pyridinium mannoside (19), 0.7 g (1.21 mmoles), dissolved slowly in 10 ml of water containing 2 g of potassium iodide with the rapid liberation of iodine. Chloroform, 10 ml, and 2 g of sodium thiosulphate were added and the mixture was shaken for two hours. The chloroform layer was washed with water and evaporated to a syrup, 0.31 g. The syrup was crystallized from ether-Skellysolve B. The n.m.r. spectrum of the crystals, m.p. 53-54°, was identical with that of D-glucal triacetate, which was therefore produced in 94% crude yield.

The pyridinium glucoside (18) did not liberate iodine under similar conditions even after one day, but on heating an aqueous solution of 18 and potassium iodide to the boiling point, iodine was liberated.

b. N-(2-Deoxy-2-iodo- β -D-glucopyranosyl)-pyridinium Perchlorate (20)

The pyridinium glucoside (18), 4 g, was dissolved in 100 ml of methanol and one ml of triethylamine. After one day, the solvents were evaporated and a crystalline residue remained which was recrystallized from water. A 72% yield, 2.25 g, was obtained. Further recrystallization from methanol with a little water gave an analytical sample, m.p. 155-157° (decomposition of the liquid phase to a black tar), $[\alpha]_D + 132.5^\circ$ (c, 1 in water), the n.m.r. spectrum shown in Fig. 15, and the o.r.d. data given in Table I. Anal. Calcd. for $C_{11}H_{15}O_8NICl$: C, 29.25; H, 3.35; N, 3.10. Found: C, 29.01; H, 3.23; N, 3.02.

An attempt to deacetylate the pyridinium mannoside under similar conditions resulted in decomposition to uncharacterized dark-brown products.

c. N-(3,4,6-Tri-O-acetyl-2-deoxy-2-iodo- β -D-glucopyranosyl)-1,4-dihydropyridine (21)

A 5.08 g sample of 18 was dissolved on warming in 100 ml of water and 40 ml of methanol. Addition of anhydrous sodium bicarbonate, 5.02 g, and sodium dithionite, 5.5 g, in 40 ml of water immediately produced a yellow coloration. The solution then became turbid and a gummy precipitate was deposited. After one hour, the gum was washed with water. It dissolved on gently warming in ethanol and, on cooling, crystals were obtained, m.p. 68.5-69.5°. The n.m.r. spectrum in chloroform initially gave a spectrum similar to that for the compound obtained on the dithionite reduction of N-(2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl)-

pyridinium bromide. (This compound (27) is described later on.) However, 21 in the chloroform solution rapidly decomposed with the liberation of iodine and the signal at approximately 7 τ disappeared in about ten minutes. A similar decomposition resulted with carbon tetra-chloride as solvent. The compound was not analysed further.

d. N-(3,4,6-Tri-O-acetyl-2-bromo-2-deoxy- β -D-glucopyranosyl)-pyridinium Perchlorate (22)

The bromonium complex (9), 19.5 g (50.2 mmoles of bromonium ion as determined by titration), reacted rapidly with D-glucal triacetate, 15.72 g (58 mmoles), dissolved in pure chloroform, to yield a fine precipitate. Recrystallization from ethanol, with a little methanol to facilitate solution, gave a product of m.p. 117-119°, $[\alpha]_D + 78.8^\circ$ (c, 1.2 in methanol). Cooling of the mother liquors resulted in a further crop of crystals which, when crystallized from methanol, melted at 152.5-155°. After drying in vacuo both lots of crystals had the n.m.r. spectrum shown in Fig. 16. Those with melting point 117-119°, on dissolving in methanol and seeding with the crystals melting at 152.5-155°, yielded crystals with the latter melting point. The crystals from ethanol, if air dried, gave an n.m.r. spectrum which showed 1.5 moles of ethanol per mole of 22. The crystals from methanol were submitted for analysis. Anal. Calcd. for $C_{17}H_{21}O_{11}NBrCl$: C, 38.47; H, 3.17; N, 2.64. Found: C, 38.24; H, 3.99; N, 2.81. The ultraviolet spectrum gave λ_{max}^{MeOH} 260 m μ (ϵ 5700). The o.r.d. data are given in Table I.

On adding ether to the filtrate, a syrup separated which

could not be induced to crystallize. The syrup was soluble in methanol and acetone but not in water or ethylacetate. After evaporation in a high vacuum, the residue, 2.58 g, gave an n.m.r. spectrum in methylene chloride very similar to that of the 2-deoxy-2-iodomannopyranoside (19) in the same solvent. The acetyl signals at 7.73τ correspond closely in chemical shift to those for 19 at 7.73 and 7.70τ . Also a doublet of spacing 10 c.p.s. at 3.48τ closely parallels the doublet for 19, spacing 10 c.p.s. at 3.43τ . The signals for the aromatic protons on the pyridinium ring of both spectra have the same appearance. Further, when the syrup was dissolved in pyridine, crystals of the 2-deoxy-2-bromoglucoside (22) were deposited. After clarification with charcoal, Darco G60, the residual syrup's n.m.r. spectrum showed a decrease in intensity of the acetyl signal at 7.73τ , relative to those at higher field, from a value of 40% of the total acetyl intensity before the pyridine was added, to 30% for the syrup obtained after the pyridine was added.

e. N-(3,4,6-Tri-O-acetyl-2-deoxy-2-iodo- β -D-glucopyranosyl)- α -picolinium Perchlorate (23)

D-Glucal triacetate, 13.7 g (50.3 mmoles), and the iodonium complex (5), 20.8 g (50.3 mmoles), were stirred in pure chloroform for 4 hours. All of 5 dissolved and an oil separated. On standing overnight, liberated iodine had turned the chloroform layer violet. The syrupy oil was sufficiently mobile to give an n.m.r. spectrum which had acetyl groups shifted downfield, with a peak centered at 7.63τ . In methanol these showed as clean signals at 7.63τ and 7.68τ . There was also a prominent signal at -0.42τ .

A hot aqueous extract of the syrup deposited crystals on cooling, m.p. 186-7°, $\lambda_{\text{max}}^{\text{MeOH}}$ 270 m μ (ϵ 8070), the n.m.r. spectrum shown in Fig. 17, and the o.r.d. data listed in Table I.

The upper phase from the reaction mixture gave an n.m.r. spectrum which corresponded to that of D-glucal triacetate.

f. N-(3,4,6-Tri-O-acetyl-2-bromo-2-deoxy- β -D-glucopyranosyl)- α -picolinium Perchlorate (24)

D-Glucal triacetate, 3.74 g (1.375 mmoles), and the bromonium complex (8), 5.313 g (1.36 mmoles from the titration of bromonium ion), gave an exothermic reaction when dissolved in chloroform. A fine precipitate was deposited. It was recrystallized from water to give needles showing strong birefringence with polarized light. At 220-221° the birefringence was distorted and at 223-4° the crystals decomposed. A 0.5 percent solution in methanol was only obtained on heating, and hence, the rotation was measured at room temperature using a supersaturated solution, $[\alpha]_{\text{D}} + 100^\circ$ (c, 0.5 in methanol). The n.m.r. spectrum is given in Fig. 18. Anal. Calcd. for $\text{C}_{18}\text{H}_{23}\text{O}_{11}\text{NClBr}$: C, 39.69; H, 4.26; N, 2.57. Found: C, 39.69; H, 4.36; N, 2.68.

g. N-(3,4,6-Tri-O-acetyl-2-bromo-2-deoxy- β -D-glucopyranosyl)-pyridinium Bromide (25)

Bromine was added slowly to D-glucal triacetate, 3 g (1.1 mmoles), dissolved in chloroform until the reaction mixture was a light red-brown color. After standing at room temperature for 20 minutes and then evaporating at reduced pressure, the residual syrup was dissolved in pyridine. The initial observed rotation was about 70° and was falling at about one degree per

minute when the solution became too opaque to take further readings. Overnight crystals were deposited. These were collected by filtration and recrystallized twice from 95% ethanol-ethyl acetate, m.p. 130-133°, $[\alpha]_D + 79.2^\circ$ (c, 1.2 in methanol), n.m.r. spectrum shown in Fig. 19, and the o.r.d. data in Table I. Anal. Calcd. for $C_{17}H_{21}O_7NBr_2 \cdot H_2O$: C, 38.58; H, 4.38; N, 2.63. Found: C, 38.50; H, 4.30; N, 2.52. The deuterium hydroxide signal in the n.m.r. spectrum has the intensity of two protons.

The filtrate was evaporated to a syrup which was triturated with chloroform. Then the syrup was dissolved in water, extracted twice with chloroform, and the aqueous phase evaporated to a syrup which gave the n.m.r. spectrum in Fig. 20 and the o.r.d. data in Table I.

2. N-Glucopyranosylpyridinium Bromide and its Derivatives

a. N-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-pyridinium Bromide (26)

Compound 26 was prepared by the method of Fischer and Raske (69). Tetra-O-acetyl-α-D-glucopyranosyl bromide (α-acetobromoglucose), 12.15 g, and phenol, 5 g, were dissolved in 27 ml of anhydrous pyridine. It was only after two months that the darkened solution solidified with crystals. These were not readily recrystallized from methyl ethyl ketone but methanol-ethyl acetate gave good crystals, m.p. 170°, n.m.r. spectrum shown in Fig. 21, $[\alpha]_D -5.9^\circ$ (c, 10 in water). The ultraviolet spectrum gave $\lambda_{\text{max}}^{\text{MeOH}}$ 259 mμ (ε22,700). Table I gives the o.r.d. data.

b. N-Tetra-O-acetyl- β -D-glucopyranosyl-1,4-dihydropyridine (27)

Compound 26, 2.2 g, dissolved in 20 ml of water, was reduced by adding a solution of 2.3 g of sodium bicarbonate and 2.35 g of sodium dithionite in 25 ml of water (70). The gummy precipitate was filtered after one hour and washed with water. It crystallized from 95% ethanol, m.p. 145° to give the n.m.r. spectrum in Fig. 22.

c. N- β -D-Glucopyranosylpyridinium Bromide (28)

Compound 26, 3.2 g, dissolved in 320 ml of 3% hydrobromic acid, was deacetylated for 15 hours at 40° (71). The solution was evaporated to a syrup which was triturated with hot chloroform and then crystallized from 95% ethanol. Two recrystallizations from ethanol-water gave 1.43 g of material, m.p. $176-177^{\circ}$, $[\alpha]_D + 45.5^{\circ}$ (c, 1.2 in water), n.m.r. spectrum shown in Fig. 23 and o.r.d. data in Table I. Anal. Calcd. for $C_{11}H_{16}O_5NBr$: C, 41.01; H, 5.01; N, 4.35. Found: C, 40.98; H, 4.87; N, 4.27.

d. N-(2,3,4,6-Tetra-O-acetyl- β -D-glucopyranosyl)- γ -picolinium Bromide (29) and the α -Anomer (30)

α -Acetobromoglucose, 3.78 g, was dissolved in 5 ml of γ -picoline and after 2 days the solution was filled with crystals. Ethyl acetate was added and the crystals removed by filtration. Recrystallization from 95% ethanol-ethyl acetate gave crystals, m.p. $202-3^{\circ}$, n.m.r. spectrum shown in Fig. 24, showing that 0.5 of a molecule of each of ethanol, ethyl acetate and water per molecule of 29 was present. After drying at high vacuum the crystals tended to decompose at 207° and melted at 208.5° , $[\alpha]_D - 10.2^{\circ}$ (c, 1 in water), o.r.d. data given in Table I.

Anal. Calcd. for $C_{20}H_{26}O_9NBr \cdot 0.5H_2O$: C, 46.80; H, 5.30; N, 2.73. Found: C, 46.95; H, 5.30; N, 2.62. The infrared spectrum in nujol of the analytical crystals contained a sharp peak at 3620 cm^{-1} and a broad peak at 3350 cm^{-1} , and this confirms the presence of hydroxyl groups.

The filtrate on standing also gave crystals. These were recrystallized from 95% ethanol-ethyl acetate to give material of m.p. 175° , $[\alpha]_D + 43^\circ$ (c, 1 in water), n.m.r. spectrum shown in Fig. 25; o.r.d. data given in Table I. Anal. Calcd. for $C_{20}H_{26}O_9NBr \cdot H_2O$: C, 45.98; H, 5.40. Found: C, 46.20; H, 5.14. The infrared spectrum in nujol of the analytical crystals contained a peak at 3480 cm^{-1} . The n.m.r. spectrum (Fig. 25) also confirmed the presence of a monohydrate as the deuterium hydroxide peak has the intensity of two protons.

e. N- β -D-Glucopyranosyl- γ -picolinium Bromide (31)

Compound 29, 0.65 g, was deacetylated in 65 ml of 3 percent hydrobromic acid for 12 hours at 40°C (71). The syrup obtained after evaporation at reduced pressure, deposited crystals from ethanol-ethyl acetate, m.p. $162\text{--}162.5^\circ$, $[\alpha]_D + 38.3^\circ$ (c, 1.2 in methanol), n.m.r. spectrum shown in Fig. 26; o.r.d. data given in Table I.

f. N- α -D-Glucopyranosyl- γ -picolinium Bromide (32)

Compound 30, 1.2 g, was deacetylated similarly, but the syrup could not be induced to crystallize. The n.m.r. spectrum is shown in Fig. 27 and the o.r.d. data are given in Table I.

3. Kinetic and Mechanistic Studies on N-Glucopyranosylpyridinium Bromide Formation

a. Reactions of Pyridine with Tetra-O-acetyl- α -D-glucopyranosyl Bromide

α -Acetobromoglucose, 35.33 g, dissolved in pyridine, 50 ml, to give a rotation after 5 minutes of 94.8° (observed), which fell to a constant value of 8.5° after one day. The pyridine was evaporated, the residual syrup was dissolved in water and then evaporated. This was repeated several times to remove the last traces of pyridine. Finally the n.m.r. spectrum of the syrup in deuterium oxide was taken, Fig. 28, indicating the presence of both the α -anomer (33) and β -anomer (25) of N-(2,3,4,6-tetra-O-acetyl-D-glucopyranosyl)-pyridinium bromide. The rotational change indicated an induction period, and hence the following systematic study was made.

(i) α -Acetobromoglucose, 0.1945 g, was dissolved in dry pyridine to give a 10 ml solution. The rotation was followed, Diag. 2, and fell from $[\alpha]_D + 194.4^\circ$ to 7.2° (the latter based on the weight of the N-glucopyranosylpyridinium bromides formed). The n.m.r. spectrum in Fig. 29 was obtained from the solution after partial evaporation of the pyridine. Then the solution was evaporated to dryness and the final traces of pyridine were removed as above. The n.m.r. spectrum in deuterium oxide is shown in Fig. 30.

(ii) Conditions exactly analogous to (i) but with 1.634 g of α -acetobromoglucose gave an initial $[\alpha]_D + 194.6^\circ$, falling to 10.3° .

(iii) When 3.436 g of α -acetobromoglucose were used the initial

$[\alpha]_D$ of 194° fell to 13.35° , n.m.r. spectrum of the reaction mixture shown in Fig. 31, and of the syrup in deuterium oxide in Fig. 32, $[\alpha]_D + 22.7^\circ$, (c, 4.3 in water). When the syrup from deuterium oxide was again dissolved in pyridine, the signal at 7.47τ reappeared.

(iv) When 1.579 g of α -acetobromoglucose and 1.353 g of tetra-n-butyl-ammonium bromide were dissolved in 10 ml of pyridine solution, the $[\alpha]_D$ fell from 191.4° to 18.4° , with the n.m.r. spectrum in deuterium oxide shown in Fig. 33.

(v) The silver complex (3), 1.518 g, and tetra-n-butylammonium bromide, 1.352 g, were dissolved in pyridine. The pyridine was evaporated and methanol was added to the residual syrup to precipitate silver bromide. Removal of silver salts by filtration through Celite and evaporation of the filtrate left 1.32 g of tetra-n-butylammonium perchlorate as a syrup. The latter and 1.586 g of α -acetobromoglucose were dissolved in 10 ml of pyridine solution, and $[\alpha]_D$ fell from 194.6° to 9.65° . The n.m.r. spectrum of the residual syrup in deuterium oxide (external TMS) had anomeric signals of about equal intensity at 3.05τ , spacing ill-defined but small, and 3.55τ , spacing about 8 c.p.s.

(vi) When 1.591 g of α -acetobromoglucose were dissolved in 5 ml of acetonitrile and the volume made up to 10 ml with pyridine, $[\alpha]_D$ dropped from 186° to 14.15° . The residual syrup gave an n.m.r. spectrum in deuterium oxide (external TMS) with anomeric signals of equal intensity at 3.02τ , spacing about 3 c.p.s. and at 3.52τ , spacing about 8 c.p.s.

(vii) The glucopyranosylpyridinium bromide (25), 0.117 g, in 5 ml

of a pyridine solution gave a constant observed rotation over 28 hours, of approximately -0.3° (traces of crystals made an accurate reading impossible).

(viii) Tetra-O-acetyl- β -D-glucopyranosyl chloride, 2 g, was dissolved in 5 ml of pyridine. After 2 minutes the rotation was -5.2° and this rose to 34.15° after 53 hours. After several days the pyridine was evaporated. The residual syrup was dissolved by shaking with equal volumes of chloroform and water. The aqueous phase on evaporation gave a syrup with the n.m.r. spectrum shown in Fig. 34. The n.m.r. spectrum of the syrup from the chloroform layer indicated it was mainly anomerized starting material as gauged by the doublet of spacing 3.5 c.p.s., at 3.70τ , identical with that for the anomeric proton of α -D-glucopyranosyl chloride tetraacetate.

(ix) α -Acetobromoglucose, 3.03 g (7.37 mmoles), was dissolved in 10 ml of pyridine and 0.89 ml of methanol, (21.8 mmoles). The observed rotation after 5 minutes was 47° and this fell to a constant value of 2.81° after 19 hours. The rotation indicated an induction period, falling at 0.086° per minute initially and at 0.147° per minute after two hours. The syrup remaining after evaporation of the solvents was equilibrated in chloroform and water. The chloroform layer was evaporated to a syrup, with the n.m.r. spectrum shown in Fig. 35, and the aqueous layer, on similar treatment, gave the n.m.r. spectrum shown in Fig. 36.

(x) The rotation of a solution of 4.44 g of α -acetobromoglucose in 10 ml of *s*-collidine did not change after 5 days, nor did the n.m.r. spectrum.

D. PREPARATION OF CARBOHYDRATE 1,2-ORTHOESTERS

1. Carbohydrate 1,2-Orthoacetates

a. α -D-Glucopyranose 1,2-(Ethyl Orthoacetate)-3,4,6-tri-acetate (34)

2,3,4,6-Tetra-O-acetyl- α -D-glucopyranosyl bromide (α -aceto-bromoglucose), 4.1 g (10 mmoles), was dissolved in 10 ml of s-collidine and 0.6 ml of dry ethanol (10 mmoles). Tetra-n-butyl-ammonium bromide, 1 g (3.1 mmoles), was added, and on heating to 50° with shaking, a homogeneous solution was obtained. Crystals of s-collidinium hydrobromide soon began to separate. After 12 hours at 50°, the almost solid reaction mixture was dissolved in the minimum chloroform and washed with just sufficient hydrochloric acid to neutralize the s-collidine, then with aqueous sodium bicarbonate and finally water. After drying the chloroform layer by filtration through chloroform-wetted filter-paper, evaporation at reduced pressure left a semi-crystalline mass. The n.m.r. spectrum, shown in Fig. 37, indicated that only the two diastereoisomers of the 1,2-orthoacetate had formed in theoretical yield, 3.8 g (10 mmoles). On recrystallizing from hot ethanol with a drop of s-collidine, and adding water just to turbidity, a heavy crystalline precipitate was obtained. The crystals were collected by filtration, washed with water and dried in vacuo. The yield of the "exo" isomer, as shown by its n.m.r. spectrum in Fig. 38, was 85%, m.p. 95-96°; reported 97-97.5°, after two recrystallizations from ethanol. When a 10 molar excess of ethanol over the α -acetobromoglucose was used, the prod-

uct still contained only 14% of the "endo" isomer.

b. α -D-Glucopyranose 1,2-(Isopropyl Orthoacetate)-3,4,6-tri-acetate (35)

Using the standard conditions above but with isopropanol in place of ethanol, a theoretical yield of the "endo" and "exo" diastereoisomers was obtained, with the n.m.r. spectrum shown in Fig. 39. Crystallization from ethanol with a trace of s-collidine, and water added to turbidity, gave an 88% yield of the "exo" isomer, m.p. 116-117°. On repeated recrystallization the m.p. was raised to 120-121°, $[\alpha]_D + 30^\circ$ (c, 2.4 in chloroform). Anal. Calcd. for $C_{17}H_{26}O_{10}$ (mol. wt. 390.4): C, 51.8; H, 6.67. Found: mol. wt. 384; C, 51.54; H, 6.82.

c. α -D-Glucopyranose 1,2-(t-Butyl Orthoacetate)-3,4,6-tri-acetate (36)

Again the above conditions were employed but with t-butanol, except that the acid washing was omitted, due to the very high sensitivity of the orthoacetate. The s-collidine was finally removed in vacuo with warming at 80° to give a crystalline mass in theoretical yield, with the n.m.r. spectrum in Fig. 40. The pure "exo" isomer was obtained on dissolving the crude crystals in hot ethyl acetate and adding Skellysolve B to turbidity. A 75% yield of the orthoester (36) m.p. 152.5-154.5°, $[\alpha]_D + 34.5^\circ$ (c, 1.6 in chloroform) was obtained. Anal. Calcd. for $C_{18}H_{28}O_{10}$ (mol. wt. 404.4): C, 53.3; H, 6.98. Found: mol. wt. 394; C, 53.1; H, 6.71.

d. α -D-Glucopyranose 1,2-(Cyclohexyl Orthoacetate)-3,4,6-tri-
acetate (37)

Using the standard conditions a syrup was obtained, which could not be induced to crystallize, but the n.m.r. spectrum, Fig. 41, indicates that essentially pure orthoester was formed.

e. α -D-Glucopyranose 1,2-(Phenyl Orthoacetate)-3,4,6-tri-
acetate (38)

(i) With phenol as the "alcohol" under the standard conditions, a syrup was obtained. The n.m.r. spectrum in Fig. 42, shows that the diastereoisomeric orthoacetates are the only products with 68% of the "exo" and 32% of the "endo" isomers.

(ii) α -Acetobromoglucose, 0.82 g (2 mmoles), and silver di-s-collidine perchlorate (1), 1 g (22.2 mmoles), were added to phenol, 0.27 g (28.7 mmoles), which had been dried by dissolving in benzene and distilling off the latter. On adding 3 ml of methylene chloride, as the reactants dissolved, silver bromide was precipitated. The reaction mixture was refluxed overnight and filtered through a bed of Celite which was washed with methylene chloride. The combined filtrate and washings were shaken with dilute sulphuric acid and sodium hydroxide and then evaporated to a syrup, 0.85 g (100% yield). The n.m.r. spectrum is shown in Fig. 43. Integration of the C-methyl signals indicated that 87% of the "exo" isomer and 13% of the "endo" were formed.

(iii) Silver di-s-collidine fluoroborate was prepared by adding an excess of s-collidine to an aqueous solution of silver fluoroborate. The precipitate was crystallized from acetone to give material of m.p. 214-218° (dec.). This silver fluoroborate

complex was used in an exactly analogous experiment to (ii) above instead of the perchlorate complex (1). The n.m.r. spectrum of the syrupy product (100% yield) is shown in Fig. 44. Some orthoacetate is indicated but crystallization from ethanol gave phenyl β -D-glucopyranoside tetraacetate (10% yield), m.p. 120-122°, undepressed on admixture with an authentic sample.

(iv) When ethanol was used in place of the phenol in (iii) above, an over 50% yield of ethyl β -D-glucopyranoside tetraacetate m.p. 105-106°, undepressed on admixture with an authentic sample, was obtained. The n.m.r. spectrum of the crude reaction syrup indicated no orthoacetate formation.

f. α -D-Glucopyranose 1,2-(Methyl Orthoacetate)-3,4,6-tri-acetate

2,3,4,6-Tetra-O-acetyl- β -D-glucopyranosyl chloride, 1.33 g (25 mmoles), and methanol, 0.404 ml (50 mmoles) in 10 ml of methylene chloride were stirred with silver acetate, 4.5 g (27 mmoles), and dicyclohexylcarbodiimide, 1.03 g (25 mmoles). The latter was added to react with the acetic acid formed in the reaction. After stirring overnight, the reaction mixture was filtered on a bed of silicic acid, and the filtrate was shaken with water, and evaporated to a syrup with an n.m.r. spectrum similar to Fig. 35, but with signals due to dicyclohexylcarbodiimide or its derivatives as well. The latter signals did not interfere with the pyranose ring protons, and the methoxyl and C-methyl peaks at 6.78 τ and 8.30 τ respectively are obviously those of the "exo" orthoacetate (Table II). No signals for the methoxyl group of the "endo" isomer were detectable.

2. Carbohydrate 1,2-Orthobenzoates

a. 1,3,4,6-Tetra-O-acetyl-2-O-benzoyl- α -D-glucopyranose (39)

1,3,4,6-Tetra-O-acetyl- α -D-glucopyranose (17), 10 g (29 mmoles), dissolved in 20 ml of dry pyridine was added to 6 ml of benzoyl chloride (51 mmoles). An immediate precipitate was obtained and the solution became hot. After 3 hours the solution was poured into saturated aqueous sodium bicarbonate and shaken until there was no further evolution of carbon dioxide. The oil was extracted with chloroform and the chloroform solution was washed with 2 N sulphuric acid and aqueous sodium bicarbonate. The syrup obtained on evaporation of the chloroform, could not be crystallized. It was therefore redissolved in chloroform and the solution was passed down a silicic acid column to purify the product from hydroxylated impurities. Still the syrup obtained could not be crystallized. The n.m.r. spectrum of the syrup is shown in Fig. 45. The integration for the aromatic protons is high by 46%.

b. 3,4,6-Tri-O-acetyl-2-O-benzoyl- α -D-glucopyranosyl Bromide (40)

The above syrup (39), 13 g, was dissolved in 50 ml of 30% hydrogen bromide in acetic acid, and 7 ml of acetic acid and 7 ml of acetic anhydride were added. After 6 hours at room temperature, the syrup obtained on evaporation at reduced pressure, was dissolved in chloroform and washed successively with water, sodium bicarbonate solution and water. The chloroform layer was evaporated to a syrup with the n.m.r. spectrum in Fig. 46. Although apparently the almost pure expected product, the syrup would not crystallize.

c. α -D-Glucopyranose 1,2-(Isopropyl Orthobenzoate)-3,4,6-tri-acetate (41)

The above syrup (40), 2.28 g, was dissolved in 4 ml of *s*-collidine and 0.251 g of tetra-*n*-butylammonium bromide and 0.47 ml of isopropanol were added. On warming to obtain a homogeneous solution, a fine precipitate appeared, and after 20 hours at 42°, the solution had set solid with crystals. The chloroform solution of the reaction mixture was washed with excess 2 N sulphuric acid, followed by aqueous sodium bicarbonate. The dark syrup obtained on evaporation of the chloroform layer had a doublet of spacing 5 c.p.s. at 4.13 τ . The pyranose ring protons give a similar pattern as that observed for the other glucopyranose 1,2-orthoesters, but the product was impure. No crystalline product was obtained.

3. Carbohydrate 1,2-Orthopivalates

a. 1,3,4,6-Tetra-O-acetyl-2-O-pivalyl- α -D-glucopyranose (42)

1,3,4,6-Tetra-O-acetyl- α -D-glucopyranose, 3 g (8.62 mmoles), in 9 ml of pyridine was treated with pivalyl chloride, 3.08 g (25.6 mmoles). After 3 hours, the product was isolated in the normal way, and crystals were obtained from the syrup on evaporation at high vacuum. Two recrystallizations from methanol-water yielded crystal plates, m.p. 109.5-110°, $[\alpha]_D + 93.2^\circ$ (c, 1.2 in chloroform), n.m.r. spectrum shown in Fig. 47. Anal. Calcd. for $C_{19}H_{29}O_{11}$: C, 52.77; H, 6.52. Found: C, 52.63; H, 6.20.

b. 3,4,6-Tri-O-acetyl-2-O-pivalyl- α -D-glucopyranosyl Bromide (43)

The above crystals (42), 1.486 g (3.44 mmoles), were dissolved in 5 ml of 30% hydrogen bromide in acetic acid, one ml of acetic

acid and one ml of acetic anhydride. After 9 hours, the product was isolated in the normal fashion. The syrup obtained, could not be crystallized, but had the n.m.r. spectrum in Fig. 48, in theoretical yield for the bromide.

c. (i) α -D-Glucopyranose 1,2-(Methyl Orthopivalate)-3,4,6-triacetate (44)

The above syrup (43), 0.55 g (1.21 mmoles), was dissolved in 2 ml of s-collidine and one ml of methanol, (24.7 mmoles), and 0.2 g of tetra-n-butylammonium bromide were added. The reaction time is significantly longer than that for the formation of orthoacetate. After one day at 60°, the reaction mixture was shaken with carbon tetrachloride and the s-collidinium bromide removed by filtration. The carbon tetrachloride filtrate was washed with excess dilute sulphuric acid and water and then evaporated to a syrup, 0.3 g (61% yield), with the n.m.r. spectrum shown in Fig. 49.

(ii) α -D-Glucopyranose 1,2-(Isopropyl Orthopivalate)-3,4,6-triacetate (45)

Using the above conditions but with isopropanol instead of methanol, the n.m.r. spectrum of the syrupy product had a doublet, spacing 5 c.p.s. at 4.17 τ . The overlapping of the isopropyl and t-butyl signals made it impossible to calculate the ratio of the two diastereoisomers.

4. Carbohydrate 1,2-Orthocarbonates

a. 3,4,6-Tri-O-acetyl-2-O-methoxycarbonyl- α -D-glucopyranosyl Chloride (46)

3,4,6-Tri-O-acetyl- β -D-glucopyranosyl Chloride (Brigl's Chloride), 20 g (61.5 mmoles), was dissolved in 20 ml of s-collidine and 100 ml of methyl chloroformate. On warming the solution, gases were evolved. Carbon dioxide and methyl chloride are presumably formed by nucleophilic attack of the chloride ion produced in the reaction on the methyl chloroformate. This reaction amounts to a decomposition of the methyl chloroformate which must therefore be added in a large excess. The reaction was carried out in a fume cupboard until almost all the methyl chloroformate had disappeared, around 4 hours. The products were extracted with carbon tetrachloride, removing the insoluble salts by filtration. The carbon tetrachloride solution was washed with dilute sulphuric acid and aqueous sodium bicarbonate, and finally evaporated to a syrup. The n.m.r. spectrum shown in Fig. 50, indicated that the anomerization had occurred as well as the esterification of the 2-hydroxyl, in 90% yield.

b. 1,3,4,6-Tetra-O-acetyl-2-O-methoxycarbonyl- β -D-glucopyranose (47)

The above syrup (46), 21 g (55 mmoles), was dissolved in 100 ml of acetic acid and 10 ml of acetic anhydride. Silver acetate, 15 g (89.8 mmoles), was added and the mixture refluxed for two hours. The silver salts were removed by filtration on Celite and the filtrate evaporated down to a semi-crystalline mass in vacuo. The ethanolic solution of the crystals was decolorized

with Darco G 60 and water added to the clear solution. Shiny needle-like crystals, m.p. 129.5-130°, $[\alpha]_D + 13.4^\circ$ (c, 1.12 in chloroform) were obtained. The n.m.r. spectrum in Fig. 51 confirms the structure. Anal. Calcd. for $C_{16}H_{22}O_{12}$: C, 47.29; H, 5.46. Found: C, 46.98; H, 5.20.

c. 3,4,6-Tri-O-acetyl-2-O-methoxycarbonyl- β -D-glucopyranosyl Chloride (48)

The above crystals (47), 0.5 g (1.23 mmoles), reacted with aluminium chloride, 0.164 g (1.23 mmoles), in 6 ml of methylene chloride over half an hour with stirring. Dry benzene, 15 ml, was added to the reaction mixture, which was passed through a bed of 1/2 g of dry silicic acid. The benzene-methylene chloride solution was washed with ice-cold water and evaporated to a crystalline mass, 0.31 g (66% yield). Recrystallization from benzene-Skellysolve B yielded material, m.p. 55-80° $[\alpha]_D + 5.45^\circ$ (c, 3 in chloroform). Recrystallization did not alter the properties of 48; but crystallization from benzene alone, followed by grinding the crystals to a fine powder before drying in vacuo for one day, raised the m.p. to 103.5-104°. The n.m.r. spectrum in deuterated chloroform (Fig. 52), indicated the presence of about one-third mole of benzene per mole of 48. Anal. Calcd. for $C_{14}H_{19}O_{10}Cl$, 0.353 (C_6H_6): C, 47.18; H, 5.20. Found: C, 47.44; H, 5.3.

d. α -D-Glucopyranose 1,2-(Dimethyl Orthocarbonate)-3,4,6-tri-O-acetate (49)

(i) The above β -chloride, 0.765 g (2 mmoles), silver di-s-collidine perchlorate (1), 0.9 g (2 mmoles), and methanol, 0.5 ml

(12.13 mmoles), were allowed to react in 3 ml of methylene chloride, stirring overnight. After the removal of insoluble salts on Celite, the filtrate was washed with aqueous sodium bicarbonate and water, and finally evaporated to a syrup, with the n.m.r. spectrum shown in Fig. 53.

(ii) The α -chloride (46), 1.31 g, tetraethyl ammonium chloride, 1.33 g, methanol, 4 ml, and s-collidine, 1 ml, gave a homogeneous solution which was thermostated at 50° for 2 days. A chloroform solution of the syrup from the reaction was washed with sufficient dilute sulphuric acid to neutralize the s-collidine, and then aqueous sodium bicarbonate. The n.m.r. spectrum of the syrup 1.05 g, obtained from the chloroform layer is shown in Fig. 54.

E. α -GLUCOSIDE FORMATION FROM ORTHOESTERS BY ACID CATALYSIS

An F and M Model 500, temperature-programmed, gas chromatograph, equipped with recorder and integrator, was used for analyses by gas-liquid partition chromatography (g.-l.p.c.) of the trimethylsilyl (tms) derivatives (72) of sugars prepared under standard conditions. An 8 ft. coiled, copper column with 0.25 in. o.d. and packed with 3% SE-52 on Chromosorb W (non-acid washed, 30-60 mesh) was found most suitable for the separation of tms derivatives of anomers. The α -glucosides always precede the β -anomers. However, the α - and β -derivatives of glucose were always present in the mixtures analysed and the trimethylsilylated α -glucose had the same retention time as those of the simple trimethylsilylated α -glucosides examined. Conditions for

separating the compounds were not realized although the effects of varying the flow rates, the polarity of the absorbent and the temperature (programmed or isothermal) were examined. Since under the standard deacetylation conditions employed, the ratio of α - to β -anomers derived from glucose in the trimethylsilylated product was constant, as determined by g.-l.p.c. whatever the source of the glucose (orthoesters or β -glucose tetraacetate), the integration value for the α -anomer could be readily determined from that of the β -form.

In preliminary experiments, known mixtures of pentaerythritol tetraacetate used as internal standard, and alkyl glucoside tetraacetates were deacetylated and converted to their tms derivatives. The correlation of mass to integrated area on chromatography, and the nature of concentration effects were determined. The peaks in any reaction run were identified by examining mixtures of known glucosides. The identifications were confirmed through n.m.r. spectra and paper chromatograms.

Retention times are not recorded since they were found dependent on the concentrations of the components in the mixture and the amount of the mixture injected. Between 30 and 50 μ l of the pyridine solution of the tms derivatives were injected. Unless otherwise stated, the column was programmed for a temperature increase of 2.9° per minute starting from 110° and holding under isothermal conditions when 250° was attained. The flow rate was approximately 100 ml of helium per minute, with an inlet pressure of 30 p.s.i.

1. The Preparation of α -Glucosides

a. Ethyl α -D-Glucopyranoside

Anhydrous p-toluenesulphonic acid was obtained from the monohydrate, by crushing the latter in ether. The ether extract was dried over phosphorous pentoxide and evaporated to a syrup in vacuo. The syrup dissolved readily in methylene chloride and the n.m.r. spectrum showed no indication of water and just a trace of ether, apart from the solvent and p-toluenesulphonic acid signals. This p-toluenesulphonic acid solution was stored sealed with a serum cap. Samples were removed with a syringe and were titrated against standard sodium hydroxide solution to determine the concentration just before use. The ethyl orthoacetate (29), 0.381 g (1.01 mmoles), was dissolved in 2 ml of methylene chloride and 0.058 ml of ethanol, (1 mmole), in a dry polarimeter tube. To the polarimeter tube was added 0.147 ml of the p-toluenesulphonic acid solution (0.2 mmoles by titration). The change in rotation (Diag. 3) was followed until it was constant. A known fraction of the reaction mixture was added to one branch of an inverted "Y-tube" sealed at one end with a high-vacuum stopcock. The solution was cooled to the dry-ice in acetone temperature and the system was evacuated. The stopcock was closed and the empty branch of the tube was cooled in the dry-ice-acetone bath. On warming to room temperature, the volatile components of the reaction mixture distilled into the cooled arm leaving a syrupy residue. The n.m.r. spectrum of the distillate was identical with that for ethyl acetate in methylene chloride, and at approximately the concentration expected should one mole

of ethyl acetate be produced per mole of orthoester. The distillate also gave a peak on g.-l.p.c. at room temperature which coincided with that of ethyl acetate.

The remaining fraction of the reaction mixture, corresponding to 0.239 g of orthoacetate initially, was evaporated to a syrup and 0.079 g of pentaerythritol tetraacetate were added. The syrup was dissolved in 2 ml of methanol and 2 ml of water. After one hour, one ml of triethylamine was added and the solution was left at room temperature for 5 hours. The syrup obtained on evaporation was dissolved in 3 ml of pyridine and 0.6 ml of hexamethyldisilazane and 0.3 ml of trimethylchlorosilane were added. On examining the products by g.-l.p.c. and from the integrations of the signals for the products relative to that of the internal standard, the actual yields from the orthoesters could be calculated on a percentage molar basis. Ethyl α -D-glucopyranoside was formed in 53% yield, ethyl β -D-glucopyranoside in 32% yield and the α - and β -glucoses in 10.6% total yield. Thus 95-96% of the orthoester was accounted for. Since the experimental error, primarily due to shifts in the base-line of the chromatograph, was from 5-10%, the analytical results were within the experimental error in accounting for the orthoester.

b. Isopropyl α -D-Glucopyranoside

(i) Using the above procedure, the reaction mixture of the isopropyl orthoacetate (30), 0.8 g (2.05 mmoles), 0.153 ml of isopropanol, (2 mmoles), and 0.31 ml of p-toluenesulphonic acid solution, (0.4 mmoles by titration), in 4 ml of methylene chloride, had reached a constant rotation after 12 hours (Diag. 3).

A fraction of the solution, to which was added a known amount of the pentaerythritol tetraacetate, was deacetylated under the standard conditions. The tms derivatives, prepared from the deacetylated syrup, were analysed by g.-l.p.c. The mixture was found to contain the α - and β -forms of isopropyl D-glucopyranoside and glucose. The yields from the orthoester were 67, 19.3 and 9.1%, respectively.

The rest of the reaction mixture was washed with aqueous sodium bicarbonate and evaporated to a syrup, which was sufficiently soluble in deuterium oxide to give the n.m.r. spectrum shown in Fig. 55. The n.m.r. spectrum in chloroform is shown in Fig. 56. A DMSO impregnated paper chromatogram gave only one spot at the origin. Under the same conditions, the isopropyl α - and β -glucoside tetraacetates had run off the paper.

A sample of the syrup, 0.111 g, was acetylated overnight in one ml of pyridine and one ml of acetic anhydride. The syrup obtained on evaporation was dissolved in chloroform, and the chloroform layer was washed with hydrochloric acid and sodium bicarbonate. The syrup from the chloroform layer had an n.m.r. spectrum almost identical to that of isopropyl α -D-glucoside tetraacetate. An ethanolic solution of the syrup was seeded with crystals of the latter and crystals were obtained of m.p. 85-86°, undepressed on admixture with authentic isopropyl α -D-glucopyranoside tetraacetate.

The syrup, 0.16 g, was also benzoylated in one ml of pyridine and one ml of benzoyl chloride. After 12 hours, a little water was added to hydrolyse the excess benzoyl chloride. Then an ex-

cess of water was added, and the oil precipitated was extracted with chloroform. The chloroform extract was washed with hydrochloric acid and sodium bicarbonate solution and evaporated to a syrup with the n.m.r. spectrum shown in Fig. 57.

(ii) A reaction mixture, in which a large excess of isopropanol was used, [thirteen moles per mole of the orthoester (35)], and trace amounts of p-toluenesulphonic acid were added until the optical rotation was not affected by further additions, was deacetylated and the tms derivatives prepared in the standard manner. The analysis by g.-l.p.c. showed that 69% of the α -isopropyl glucoside had formed along with 20% of the β -anomer and 15% of glucose. The total orthoester accounted for was 104%, which is within experimental error.

(iii) A further experiment with picric acid as the catalyst was carried out. To the isopropyl orthoacetate (35), (0.985 mmoles) and isopropanol, (1.05 mmoles), in 2 ml of methylene chloride, were added successive amounts of about 0.015 mmoles of dry picric acid over a period of 3 days until 0.07 mmoles had been added. The n.m.r. spectrum indicated that 30% of the orthoacetate remained unchanged. This amount was estimated from the relative intensities of the C-methyl signal at 8.3τ (external TMS) and those of the acetyl groups. Addition of pentaerythritol tetraacetate to serve as an internal standard, deacetylation and preparation of the tms derivatives under the standard conditions gave a product which, on analysis by g.-l.p.c. was found to correspond to a 34% yield of isopropyl α -D-glucopyranoside and a 10% yield of the β -anomer. Forty percent of the product was glucose.

c. t-Butyl α -D-Glucopyranoside

- (i) A reaction of the t-butyl orthoester (31), 0.802 g (1.98 mmoles), t-butanol, 0.12 g (1.62 mmoles), and 0.3 ml of p-toluenesulphonic acid solution (0.41 mmoles by titration) in 4 ml of methylene chloride, was followed polarimetrically. The observed rotation rose from 2° to 4.37° within two minutes after adding the p-toluenesulphonic acid solution. A maximum of about 13.03° was reached in 2 hours. The rotation then fell to a constant value of 11.67° in the next 12 hours. A portion of the reaction mixture was distilled as in the ethyl orthoacetate (34) reaction, and the n.m.r. spectrum was taken. The products indicated were t-butanol [8.77τ , 8.78τ in carbontetrachloride (73)], t-butyl acetate [8.58τ and 8.08τ , identical with authentic t-butylacetate in methylene chloride] and isobutylene [8.28τ and 5.33τ , 8.3τ and 5.4τ in carbontetrachloride (73)]. The molar ratios of these compounds were 1.37: 1: 1.5, respectively. A 32% yield of t-butylacetate was indicated by the relative intensities of the signal for the t-butyl group in t-butyl acetate and the total of the signals for acetyl groups in the n.m.r. spectrum of the reaction mixture. Analysis by g.-l.p.c., after preparation of the tms derivatives under the standard conditions, was unsatisfactory due to overlapping peaks, but glucose was a principle product as confirmed by paper chromatography of the deacetylated syrup.
- (ii) The t-butyl orthoester (36), 0.736 g (1.82 mmoles) and isopropanol, 0.153 g (2.55 mmoles), were dissolved in 2.4 ml of methylene chloride. The observed rotation was 3.62° . Picric acid, 10 mg, was added and within 1.5 minutes the rotation was

7.13° and, after 29 hours, it rose to 15.8°. At this time, an n.m.r. spectrum of a sample of the reaction mixture had a signal at 8.31 τ . The C-methyl groups for the t-butyl (36) and isopropyl orthoesters (35) give signals at 8.22 τ and 8.3 τ , respectively, in methylene chloride. The intensity of the signal at 8.31 τ relative to the sum of the intensities of this signal and the acetyl-group signals indicated that 42% of orthoester was still unreacted. One drop of s-collidine was added to the sample which was washed with water and evaporated to a syrup. The syrup was dissolved in ethyl acetate and Skellysolve B added almost to turbidity. A crystal seed of the isopropyl orthoacetate (35) aided crystallization of material with the melting point of 35 and undepressed by mixing with 35.

To the main reaction mixture there was added a further 10 mg of picric acid. The rotation rose to 21.44° after 20.5 hours. The addition of 13 mg more of picric acid raised the rotation to 22° after 3 hours. At this time, the n.m.r. spectrum of the reaction mixture contained no signals attributable to orthoesters. Addition of 3 drops of s-collidine resulted in an intensification of the yellow color of the solution, which was washed with water, and evaporated to a syrup. A benzene solution of the yellow syrup was passed down an alumina column to remove the picric acid. On evaporating the colorless benzene eluate from the column, the yellow color reappeared. Therefore the syrup was again passed through an alumina column. Again, the yellow color reappeared on evaporation of the colorless eluate. The syrup was deacetylated by the Zemplen method with sodium methoxide in methanol,

and the deacetylated syrup chromatographed on 40 g of Celite (66). The stationary phase was water saturated with n-butanol and the irrigant was n-butanol saturated with water. Fractions of 25 ml of eluate were collected. Fractions 5 to 12 inclusive yielded crystals m.p. 153° , $[\alpha]_D + 131.3^{\circ}$ (c, 1.3 in water). t-Butyl- α -D-glucopyranoside is reported (74) to have a m.p. $150-152^{\circ}$, $[\alpha]_D + 132^{\circ}$. The n.m.r. spectrum was in complete agreement with that expected for this structure. The yield of the glucoside was 47%. Paper chromatography of the crystals revealed a single spot, $R_G = 5.1$. Fractions 13 to 14 also contained material with $R_G = 5.1$ as well as a slightly slower band. Fractions 15 to 62 were combined and on paper chromatography showed at least 5 bands, the one with strongest intensity corresponding to $R_G = 3.1$ as revealed with the silver nitrate spray.

d. Dissacharide Formation

(i) The isopropyl orthoacetate (35), 0.958 g (2.45 mmoles), in 3 ml of methylene chloride had an initial observed rotation of 5.97° . On adding 0.0275 g (0.145 mmoles) of triethyloxonium fluoroborate (75), the rotation rose within one minute to 7.75° and after 25 hours to 16.42° when the rotation appeared almost constant. When the rotation was 9.7° an n.m.r. spectrum of a sample of the reaction mixture was taken. The sharp signals at 8.28τ and 8.45τ (external TMS) are most likely the orthoacetate groups of the two possible diastereoisomers. The intensities indicated only 20% of the orthoester had reacted. A further 0.026 g (0.137 mmoles) of the fluoroborate was added and the rotation rose to 25.1° in the next 6 hours. Finally on addition

of 0.008 g (0.042 mmoles) of the fluoroborate, the rotation fell to 24.9° in half an hour and after a further 14 hours it rose to 26.53° . The solution was slightly discolored and its n.m.r. spectrum had no C-methyl signal at 8.30τ . The methylene chloride solution was washed with aqueous sodium bicarbonate and water, and then evaporated to a syrup, 0.73 g, with the n.m.r. spectrum shown in Fig. 58. The integration of the isopropyl signals indicated that the maximum isopropyl glucoside formed was 29%, when the acetyl peak integration is assumed to correspond to 12 protons. When an attempt was made to crystallize the syrup from ethanol-water, sticky crystals were obtained. These were boiled in ether and isolated by filtration as a fine white powder, 20 mg, m.p. $280-290^\circ$, $[\alpha]_D + 228^\circ$ (c, 0.75 in chloroform), and the n.m.r. spectrum shown in Fig. 59. The remaining syrup from the reaction had $[\alpha]_D + 109^\circ$ (c, 1.6 in chloroform). The syrup was deacetylated by the Zemplen method. A paper chromatogram of the deacetylated syrup was developed with the periodate-permanganate spray. A faint trace of glucose was indicated but an intense band moving at the same rate as the compound in section (ii) below, of $R_G = 0.22$, appeared to comprise the bulk of the product.

(ii) Triethyloxonium fluoroborate, 0.964 g (5.07 mmoles), and isopropanol, 0.38 ml (4.96 mmoles), were dissolved in 2 ml of methylene chloride to give a total volume of 3.2 ml. This solution, 0.1 ml (0.156 mmoles of hydrogen fluoroborate) was added to a solution of the isopropyl orthoacetate (35), 1.39 g (3.56 mmoles), in 4 ml of methylene chloride. The rotation of the mixed solutions rapidly rose from 6.84° initially to 9.56° in one minute, and then

after 21 hours to 14.7° . After another 0.1 ml of the hydrogen fluoroborate solution was added, a further rapid rise in rotation within 3 minutes to 17.8° was observed, and in the next 21 hours, the rotation rose to 24.93° . To the solution was added the weakly basic resin Rexyn AG3 (OH). After shaking the mixture for 10 minutes, the resin was removed by filtration and the filtrate was evaporated to a syrup, 1.16 g. The syrup had an n.m.r. spectrum almost identical to that in (i) above, Fig. 58. The syrup could not be induced to crystallize, even on seeding with the crystals of m.p. $280-290^\circ$ in (i) above. A sample of the syrup was deacetylated by the Zemplen method, and a paper chromatogram of the deacetylated syrup revealed no bands when sprayed with the silver nitrate spray. When the paper chromatogram was run for 2 days and sprayed with the periodate-permanganate spray there was a band at the origin but the main band had an R_G value of 0.22. A faint band was observed at $R_G = 0.77$.

e. The Reaction of the Orthocarbonate (49) with p-Toluenesulphonic Acid.

The syrupy dimethyl orthocarbonate (49), (Fig. 53), 0.414 g in 3 ml of methylene chloride, was treated with 0.3 ml of the p-toluenesulphonic acid solution, (0.42 mmoles by titration). The observed rotation after 2 minutes was 5.3° and this rose to a maximum of 8° after 3 hours and finally dropped to 6.75° after the next 19 hours. The n.m.r. spectrum of the reaction mixture (external TMS) contained a sharp signal at 6.18τ , with an intensity of about 60% of the total acetyl intensity attributable to dimethyl carbonate. Signals of approximately equal but very low

intensity at 6.43τ and 6.51τ are likely methoxyl peaks. The solution was evaporated to a syrup and the n.m.r. spectrum in methylene chloride (internal TMS) contained signals at 6.43τ and 6.53τ of equal intensity. The intensity of a signal at 6.17τ was approximately equal to the sum of these intensities. The syrup was treated in the usual manner to obtain an analysis by g.-l.p.c. but the tms derivatives were poorly resolved.

2. Mechanistic Investigations

a. An Improved Synthesis of 3,4,6-Tri-O-acetyl-1,2-anhydro- α -D-glucopyranose ("Brigl's Anhydride")

Crude 3,4,6-tri-O-acetyl- β -D-glucopyranosyl chloride, 7.4 g (22.8 mmoles), m.p. $130-133^\circ$, was suspended in 60 ml of dry benzene and 2 ml of diethylamine by shaking for $1/2$ hour. The solution was filtered through a bed of 5 g of dry silicic acid and the filtrate was evaporated to a syrup, 1.43 g. The syrup rapidly crystallized from ether-Skellysolve B and 1.3 g of "Brigl's Anhydride", m.p. $56.5-57^\circ$ was obtained. The precipitate on the silicic acid bed was collected and reacted further in 60 ml of benzene and 5 ml of diethylamine for one hour. As above, 4.49 g of syrup was obtained which deposited 3.22 g of crystals, m.p. $55-56^\circ$ from ether-Skellysolve B. The total yield of "Brigl's Anhydride" was 70%.

b. The Reaction of "Brigl's Anhydride" with p-Toluene-sulphonic acid

The doublet of spacing 2 c.p.s. at 6.95τ assigned to the proton on carbon-2 in the n.m.r. spectrum of "Brigl's Anhydride" in methylene chloride is conveniently situated for reaction

studies by n.m.r. spectroscopy. When one mole of p-toluenesulphonic acid is added to one mole of "Brigl's Anhydride", in less than one minute, the time taken to scan from 6τ to 8τ , the doublet had disappeared. No well-defined anomeric signal corresponding to a tosylate could be found but a rough signal at 4τ is observed (Fig. 60). If 0.2 moles of p-toluenesulphonic acid are added, the intensity of the 2-proton is reduced by about 20% and then takes about 2 days to finally disappear.

The rotation was also followed. "Brigl's Anhydride", 0.302 g (1.05 mmoles), in 2 ml of methylene chloride had an observed rotation of 9.1° , constant over 20 minutes. On adding 0.18 ml of p-toluenesulphonic acid solution (0.4 mmoles as determined by titration), within 2 minutes the rotation was 15.59° and it then rose steadily during 6.8 hours to 20.32° . On adding a further 0.18 ml of p-toluenesulphonic acid solution, the rotation fell to 19.7° but was rising steadily when the solution became too discolored to take a reading. To this solution, 0.2 ml of diethylamine was added and it was then filtered through a bed of dry silicic acid. Elution with methylene chloride gave no product, but 10% methanol in chloroform as eluant gave 0.416 g of syrup. The n.m.r. spectrum of the syrup indicated diethylamine hydrogen p-tosylate as an impurity, but on washing a chloroform solution of the syrup with water and aqueous sodium bicarbonate, the syrup thus obtained from the chloroform layer, 0.306 g, had the n.m.r. spectrum shown in Fig. 61.

When 1 mmole of "Brigl's Anhydride" in 2 ml methylene chloride was treated with 0.2 mmoles of p-toluenesulphonic acid in

each of 5 additions at intervals of 3 minutes, jumps in rotation of 3.25° , 3.5° , 3.25° , 3° and -0.25° were observed, from an initial rotation of 9.27° . The rotation then dropped from a maximum of 22.25° to around 14° after 3 hours when the solution became too dark to take a reading.

c. The Formation of Glucosides from "Brigl's Anhydride" with p-Toluenesulphonic Acid as the Catalyst

(i) Ethyl Glucoside Formation.

"Brigl's Anhydride", 0.2974 g (1.03 mmoles), reacted with 0.06 ml of ethanol, (1.04 mmoles), in 2 ml of methylene chloride in the presence of 0.09 ml of p-toluenesulphonic acid solution, (0.2 mmoles by titration). The observed rotation rose from 9.22° to 14.25° in 15 minutes and then gradually fell to 9.7° after 21 hours. The standard procedure used in the acid-catalysed ortho-ester reactions was used to analyse the reaction products by g.-l.p.c. The ratio of α - to β -ethyl glucosides was 40.8 to 59.2.

A portion of the reaction syrup was reacetylated and the n.m.r. spectrum of the acetylated material is shown in Fig. 62. It confirms the g.-l.p.c. analysis. Of the two partially overlapping triplets at about 8.8τ , that at higher field is due to the β -anomer by comparison with the spectra of authentic samples of the ethyl α - and β -D-glucoside tetraacetates.

Another portion of the reaction syrup was deacetylated and the paper chromatogram revealed a band corresponding to the ethyl α - and β -glucosides. After 3 days development of the chromatogram, additional spots were revealed (silver nitrate

spray) with $R_G = 0.0724$ (weak), 0.296 (strong), 0.56 (weak).

(ii) Isopropyl Glucoside Formation

Exactly similar conditions were used as above, "Brigl's Anhydride", 0.3073 g (1.065 mmoles), 0.1 ml of isopropanol, (1.3 mmoles), and 0.1 ml of p-toluenesulphonic acid solution (0.235 mmoles by titration), in 2 ml of methylene chloride. The rotation rose rapidly to a maximum of around 14° in 15 minutes and slowly decreased to 10.38° after 22 hours. The usual procedure to obtain an analysis by g.-l.p.c. showed the % ratio of α - to β -isopropyl glucoside to be 41 to 59. To determine the reproducibility of the reaction another run with "Brigl's Anhydride", 0.31 g, isopropanol, 0.1 ml, p-toluenesulphonic acid solution 0.1 ml, (0.26 mmoles by titration), was carried out in 2 ml of methylene chloride for 24 hours. On analysis by g.-l.p.c. the % ratio of α - to β - was 42.5 to 57.5. In both the above reactions, the syrupy reaction products produced n.m.r. spectra in chloroform (Fig. 63) similar to those (Fig. 56) from corresponding ortho-ester reactions. Acetylation of the syrups gave the n.m.r. spectra expected for mixtures of α - and β -glucoside tetraacetates as judged by direct comparison with the spectra obtained from authentic samples of the isopropyl α - and β -glucopyranoside tetraacetates. The relative intensities of the signals from the methyl groups of the isopropyl group and the signals from the acetoxy groups indicated that the isopropyl tri-O-acetyl- α - and β -D-glucopyranosides were formed in 87% yield. Therefore, only 13% of the 'Brigl's Anhydride' could have polymerized. Paper chromatograms of the deacetylated syrup revealed a band, not well resolved, cor-

responding to authentic isopropyl α - and β -D-glucosides. When the chromatogram was developed for 3 days, additional spots (silver nitrate spray) were found at $R_G = 0.079$ (weak), 0.296 (strong) and 0.59 (weak).

d. Reactions of Orthoesters with p-Toluenesulphonic Acid

The isopropyl orthoester (35), 0.8 g (2.05 mmoles), in 2 ml of methylene chloride was treated with one ml of p-toluenesulphonic acid solution (1.725 mmoles by titration). The rotation rose from about 6° to 24.75° in 50 minutes and then gradually fell. The solution became too discolored to read. After 3 hours, the methylene chloride solution was washed with aqueous sodium bicarbonate, and then evaporated to 0.472 g of a syrup. The syrup was not eluted by chloroform from a 5 g bed of silicic acid but was by 10% methanol in chloroform. The syrup thus obtained was re-acetylated to yield a syrup with the n.m.r. spectrum shown in Fig. 64. A DMSO impregnated paper chromatogram showed a band only near the origin under conditions where the isopropyl glucoside tetraacetates had run off the paper.

In a similar reaction 1.96 mmoles of 35 and 0.31 ml of p-toluenesulphonic acid solution, (0.4 mmoles by titration) in 4 ml of methylene chloride gave the polarimetric rate shown in Diag. 3. After 23 hours a known fraction of the reaction mixture was treated in the usual manner to obtain an analysis by g.-l.p.c. The integrations relative to the internal standard of pentaerythritol tetraacetate indicated 21% of isopropyl α -D-glucoside, 4.6% of the β -anomer and 27% of glucose were formed. An n.m.r. spectrum of the reaction solution had a peak at 8.27τ ,

(external TMS), which could be assigned to unreacted orthoacetate (35).

e. Treatment of Isopropyl β -D-Glucoside Tetraacetate with Acids

Isopropyl β -D-glucoside tetraacetate (2 mmoles), and 0.2 ml of p-toluenesulphonic acid solution (0.354 mmoles by titration) in 4 ml of methylene chloride did not change in rotation after 3 days. Isopropanol, 1.5 ml (19.6 mmoles), was added but the reaction remained constant. The solution was washed with aqueous sodium bicarbonate, evaporated to a syrup and readily crystallized from ethanol to regenerate the β -glucoside, m.p. and mixed m.p. 136°. In a similar way, it was shown that picric acid did not cause reaction of the β -glucoside.

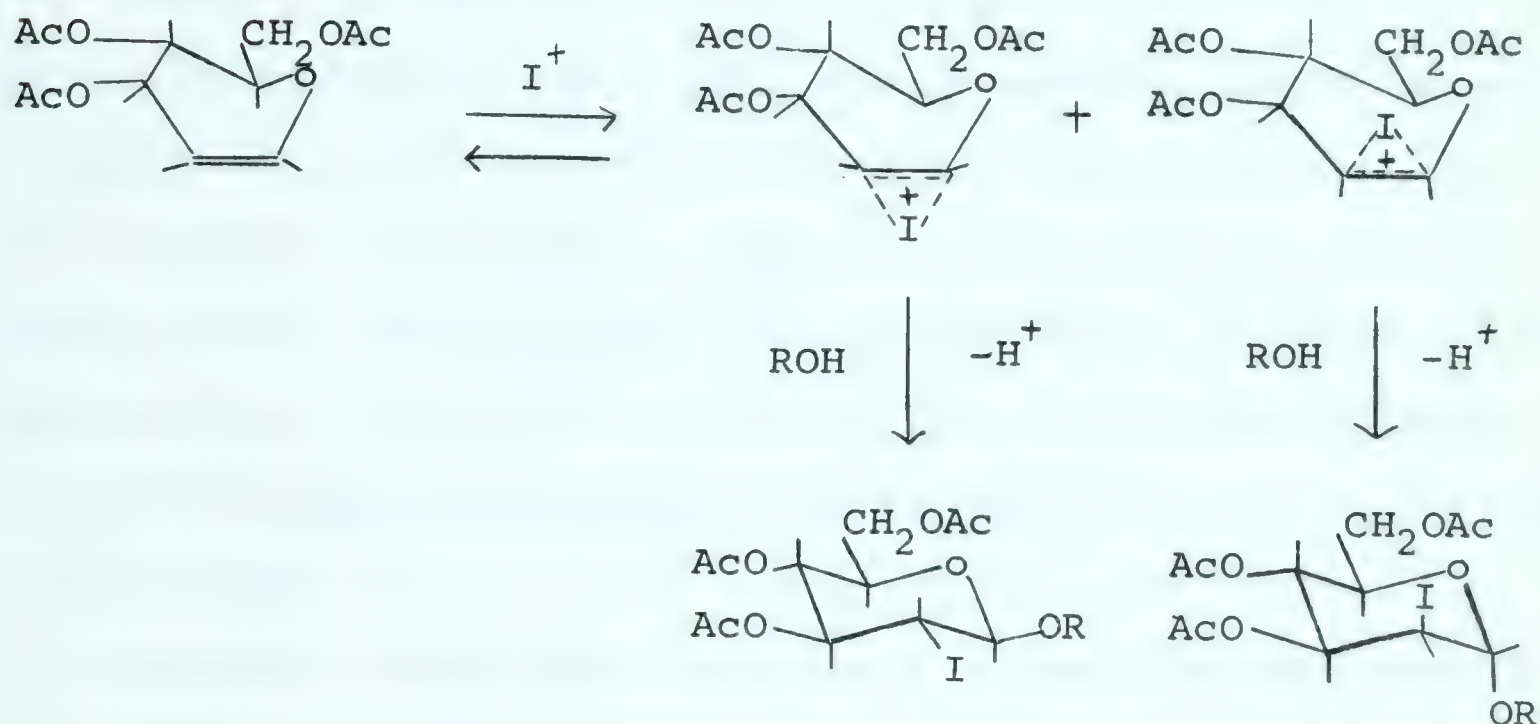
f. Diastereoisomers of Orthoesters

When the isopropyl orthoacetate (35), 0.704 g (1.8 mmoles), was dissolved in 2 ml of methylene chloride containing picric acid, 0.003 g (0.0013 mmoles), within one minute the observed rotation rose from 6° to 6.52°. After 9.5 hours the rotation was 8.49° and a further 0.003 g of picric acid was added. In the next 2 minutes the rotation rose to 8.78° and to 9.2° during the next 14 hours. The addition of a trace of isopropanol (one μ l) did not significantly alter the rotation. The n.m.r. spectrum of the reaction mixture, Fig. 65, has the C-methyl signals characteristic of the "exo" and "endo" orthoacetates (Fig. 39) at 8.31 τ and 8.47 τ . The intensity of the C-methyl signals relative to the total acetyl and C-methyl signals indicates 93% of the mixture is composed of orthoacetate.

DISCUSSION

A. THE PREPARATION OF GLYCOSIDES USING HALONIUM IONS

Initially this research was an extension of the work of Lemieux and Levine (44). The mechanism postulated for the production of 2-deoxy-2-iodoglycosides is shown in Scheme I.



Scheme I

The positive iodine, generated by the reaction of silver perchlorate with iodine, reversibly forms a complex with D-glucal triacetate. Two possible stereoisomers are formed, and these undergo nucleophilic attack by the alcohol at carbon-1 exclusively, due to partial delocalization of the positive charge

onto the ring oxygen. Only two 1,2-trans-adducts are thus expected, which will have the β -gluco- and α -manno-configurations as shown. Silver perchlorate and *s*-collidine were the preferred reagents as they are unlikely to interfere in the nucleophilic attack by the alcohol on the iodonium-olefin complex.

It was found that the larger the alcoholic grouping, the greater was the yield of the α -manno-configuration. When methanol was the alcohol a 55% yield of the α -mannoside was obtained, but with *t*-butanol an 85% yield, as determined by the integration of the n.m.r. spectra of the crude reaction syrups. Since the yields of glycosides were virtually quantitative when equimolar amounts of the alcohol and D-glucal triacetate were used, an obvious extension of the reaction was to the preparation of 2-deoxy-2-iodo-disaccharides. It was expected that the α -manno-configuration should be formed predominantly from the observations on the above simple alcohols.

It is well known that cyclohexene oxides of fixed conformation undergo opening on nucleophilic attack to yield the diaxial product in preference to the diequatorial product. This property is known as the F \ddot{u} rst-Plattner rule (68) and has been attributed to the steric and electronic demands for the nucleophilic attack. Assuming that the iodonium-olefin complexes are cyclic as indicated in the above formulae and if the rate controlling step is the attack of the cyclic iodonium ion by the alcohol, for reasons of the F \ddot{u} rst-Plattner rule, it could be expected that the preferred route of reaction would be to give the 1,2-diaxial product (α -D-manno-configuration). The α -D-manno isomer was in fact the

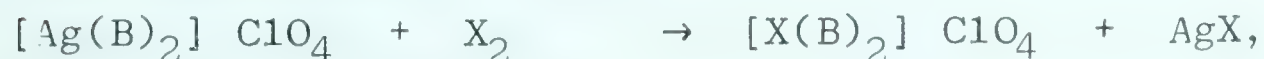
main product of the reaction both when methanol and t-butanol were used (44). The extent of the reaction leading to the β -D-glucos configuration (diequatorial product) was great as compared to those normally observed in reactions of cyclohexene oxides. The participation of the ring-oxygen may account for this difference. The fact that the attack by alcohol was entirely at carbon-1 requires that the ring-oxygen helps stabilize the transition states for these reactions, as already mentioned. Consequently, these reactions are certainly not analogous to reactions of cyclohexene oxides. In fact it is possible that the diequatorial product is primarily due to the stability of the oxocarbenium ion which may form as an intermediate in the reaction. The greater yield of the diaxial product using t-butanol suggests that diaxial opening is less sterically demanding than is the route of reaction which leads to diequatorial product.

Any speculation on the possibility of thermodynamic control, for example by the anomeric effect (14,15), can be considered only when the relative stability of the two configurations formed is known (see p. 107).

In preliminary experiments, finely ground silver perchlorate was used but it was found to be unsatisfactory on account of insoluble silver iodide coating the silver perchlorate crystals. The solubility of silver perchlorate in ethylene carbonate permitted a homogeneous reaction but increased the problems concerned with eliminating traces of water from the reaction mixture and also made the isolation of the product more difficult.

Carlsohn (76) had prepared positive iodine complexes with s-collidine such as the hydroxide corresponding to the formula $[I(s\text{-collidine})_{3.5}]OH$. In a later paper (77) he described the formation of bromonium dipyridine perchlorate, and referred to iodonium di-2,6-lutidine nitrate and the complex with s-collidine, $[I(s\text{-collidine})_{3.5}]NO_3$.

The general methods used in this thesis to prepare the complexed halonium perchlorates for use in Prevost-type reactions may be summarized as follows:



where B is an aromatic heterocyclic amine, and X_2 is a halogen molecule. The first stage was carried out in aqueous solution and quantitative yields of the complexed silver perchlorate were obtained with complete metathesis of the anion. The crystalline product did not give a brown-ring test for nitrate. As expected from the highly reactive state of positive halogens, the second

stage, in which the halonium complex was produced, was more difficult to carry out. The problem of finding a suitable solvent to dissolve the silver complex and yet which did not react readily with halonium ions, necessitated the rapid isolation of crystalline products if good yields of uncontaminated material were to be obtained. The stability and solubility of the complexes varied widely. For example, bromonium di-s-collidine perchlorate (7) is soluble enough in CH_2Cl_2 to give an n.m.r. spectrum, Fig. 1. The partial delocalization of the positive charge on bromine over the aromatic rings is evidenced by the deshielding of the protons relative to the chemical shifts of s-collidine in chloroform. Iodonium di-s-collidine perchlorate (4) is much less soluble in chloroform. It also appears less stable than the bromonium complex (7) since it decolorizes on standing in air with the liberation of iodine. The bromonium complex (7) on the other hand still gives good analyses for positive bromine after one month. If the complexes with pyridine are considered, it is the iodonium complex (6) which is more stable than the bromonium one (9). One would expect the bromonium complexes to be the less stable, but s-collidine is a stronger base than pyridine which will help minimize differences in stability. Also, in the iodonium complex (4) the 2- and 6-methyl groups on s-collidine will interact more strongly with the iodine than they will with the bromine in the complex (7). This may account for the unexpected stability of 7. In all cases, the analysis was by the titration of iodine liberated when aqueous potassium iodide is added to the complex dissolved in methylene chloride (78). The analysis always corresponded

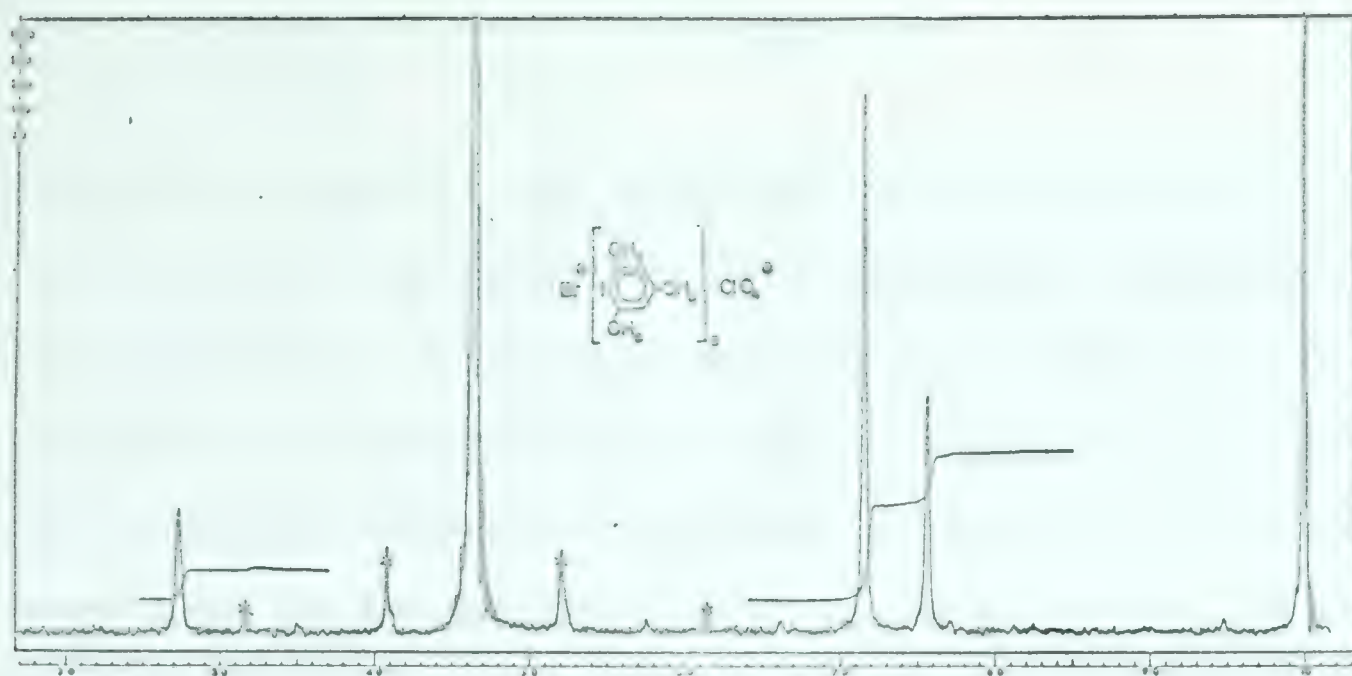


Fig. 1. Bromonium Di-s-collidine Perchlorate (7) (Methylene Chloride).

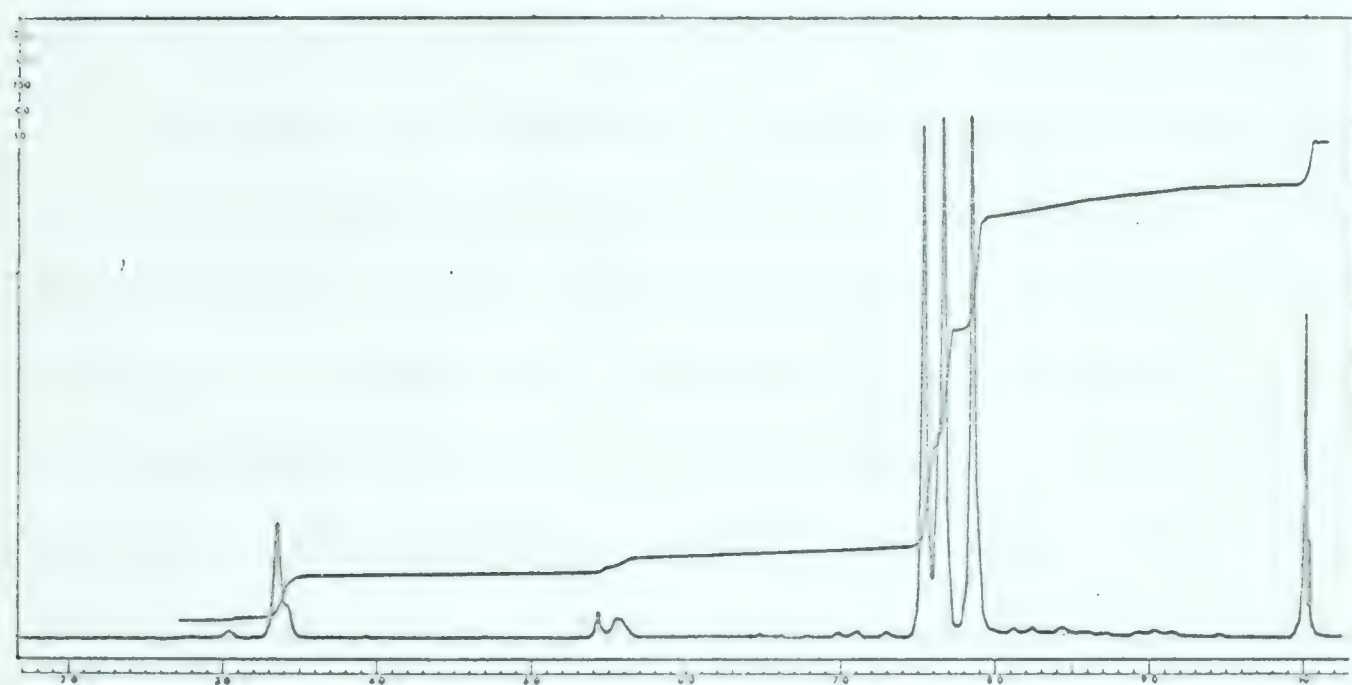


Fig. 2. The Product of the Chlorination of s-Collidine (Neat).

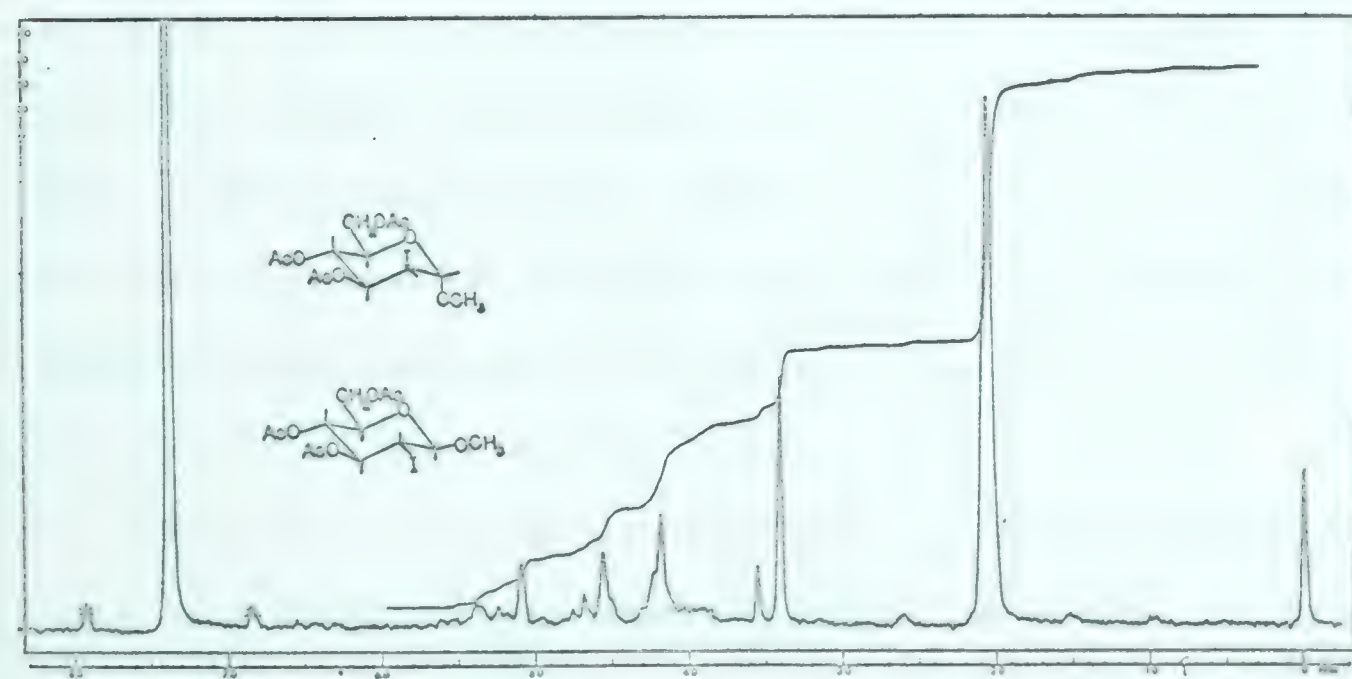


Fig. 3. Methyl 3,4,6-Tri-O-acetyl-2-deoxy-2-iodo- α -D-mannopyranoside (10) and the Corresponding β -Glucoside (11) (Chloroform).

closely to that of two molecules of the base per positive halogen, even in the case of s-collidine complexes, compounds for which Carlsohn (76,77) usually obtained 3.5 molecules. There is a strong tendency for unipositive halogens to assume a coordination of two. For example, iodonium dipyridine nitrate is conducting in solution but iodonium monopyridine nitrate is not (79). It is possible that Carlsohn's compounds contained molecules of s-collidine solvated in the crystals or s-collidinium salts as impurities.

Uschakow and Tchistow (80) prepared various halonium complexes and later they isolated chloronium dipyridine nitrate (81). When we attempted to prepare chloronium di-s-collidine perchlorate, all that was obtained was a mixture of s-collidinium perchlorate and chlorinated s-collidine. The mixture of chlorinated s-collidine had one major component as shown by vapour phase chromatography, and the n.m.r. spectrum, Fig. 2, indicated that this was 3-chloro-s-collidine. The three main peaks between 7.5τ and 8τ are readily assigned to the methyl groups, now that each one is in a different environment. The signal at 3.35τ corresponds to one ring proton. The signals of low intensity at about 5.5τ are most likely due to chlorination of the methyl groups. Benzyl chloride in carbon tetrachloride has an n.m.r. spectrum with the methylene absorption at 5.5τ (73).

Pyridine is less susceptible to electrophilic substitution than s-collidine, and when attempts were made to prepare chloronium di-pyridine perchlorate by the standard route, although no crystalline product was isolated, no evidence was obtainable of chlorination of the pyridine ring.

In order to test the products of the reactions when complexed halonium perchlorates were used instead of the silver salt and halogen in the modified Prevost reaction of Lemieux and Levine (44), the iodonium and bromonium di-s-collidine perchlorates were treated with D-glucal triacetate in the presence of one mole-equivalent of methanol with chloroform as the solvent. The reaction is essentially homogeneous since the complexes are appreciably soluble in chloroform. An 82% yield of the product with the α -manno-configuration was obtained in the reaction with the iodonium complex (4). Since the reaction was carried out in chloroform instead of benzene (44) the higher yield of the α -manno-isomer could be attributed to a solvent effect but this is unlikely since both solvents have low dielectric constants of 2.284 (benzene) and 4.806 (chloroform) at 20°C. In view of the strong tendency of halonium ions to have a coordination number of two (79), speculations as to the possibility of s-collidine being complexed in the transition state, when iodonium complexes are employed, may be entertained. Lemieux and Fraser-Reid (45) showed that the presence of s-collidine in the iodomethoxylation of D-glucal triacetate in methanol using iodine and silver acetate, also increased the yield of the α -manno-isomer.

The n.m.r. spectrum (Fig. 8) of the product formed using the bromonium complex showed signals for three different methoxyl groups; 6.43, 6.53 and 6.56 τ . A comparison of the spectrum shown in Fig. 8 with that of Lemieux and Fraser-Reid (45) confirmed that the product is mainly a mixture of methyl 3,4,6-tri-O-acetyl-2-bromo-2-deoxy- α -D-mannopyranoside (14) and the corresponding

β -glucoside (15). The major component, methoxyl signal at 6.56τ was compound 14 (45). The methoxyl signal at 6.43τ corresponds to the minor component 15. The trace of product having a methoxyl signal at 6.53τ is thought to arise from the α -anomer of 15.

In the extension of the reaction to the synthesis of disaccharides the "alcohol" used was 2,3,4,6-tetra-O-acetyl- β -D-glucose. The 2-deoxy-2-iododisaccharide heptaacetates expected were not obtained crystalline but deacetylation with triethylamine in aqueous methanol (82) yielded crystalline β -D-glucopyranosyl 2-deoxy-2-iodo- α -D-mannopyranoside (12). The structure of 12 was determined by its physical and chemical properties and its reduction to a 2-deoxy sugar, in the following manner.

Elemental analysis corresponded to a molecular formula $C_{12}H_{21}O_{10}I \cdot H_2O$. The ultraviolet spectrum $\lambda_{\max}^{\text{MeOH}}$ 255 $m\mu$ ($\epsilon 470$) confirmed the presence of the C-I bond, by comparison with that of methyl 2-iodo-2-deoxy-3,4,6-tri-O-acetyl- α -D-mannopyranoside, $\lambda_{\max}^{\text{MeOH}}$ 250 $m\mu$ ($\epsilon 770$). The n.m.r. spectrum of 12, after exchange of hydroxyl protons in deuterium oxide, Fig. 4, gave a signal at 4.35τ with a very small spacing of the order of 0 - 1 c.p.s. It seemed most likely that the signal arose from the anomeric proton of an α -manno-moiety. It is found generally, that the anomeric protons of α - and β -glucopyranosyl derivatives have spacings of 3.0 - 3.6 c.p.s. and 7 - 8 c.p.s., respectively. Although the spacings for the anomeric protons of α - and β -mannopyranosides are both in the order of 1 c.p.s., the mechanistic considerations together with the results obtained using methanol as the alcohol are in favor of the α -manno-configuration. This configuration



Fig. 4. β -D-Glucopyranosyl 2-Deoxy-2-iodo- α -D-mannopyranoside (12) (Deuterium Oxide).

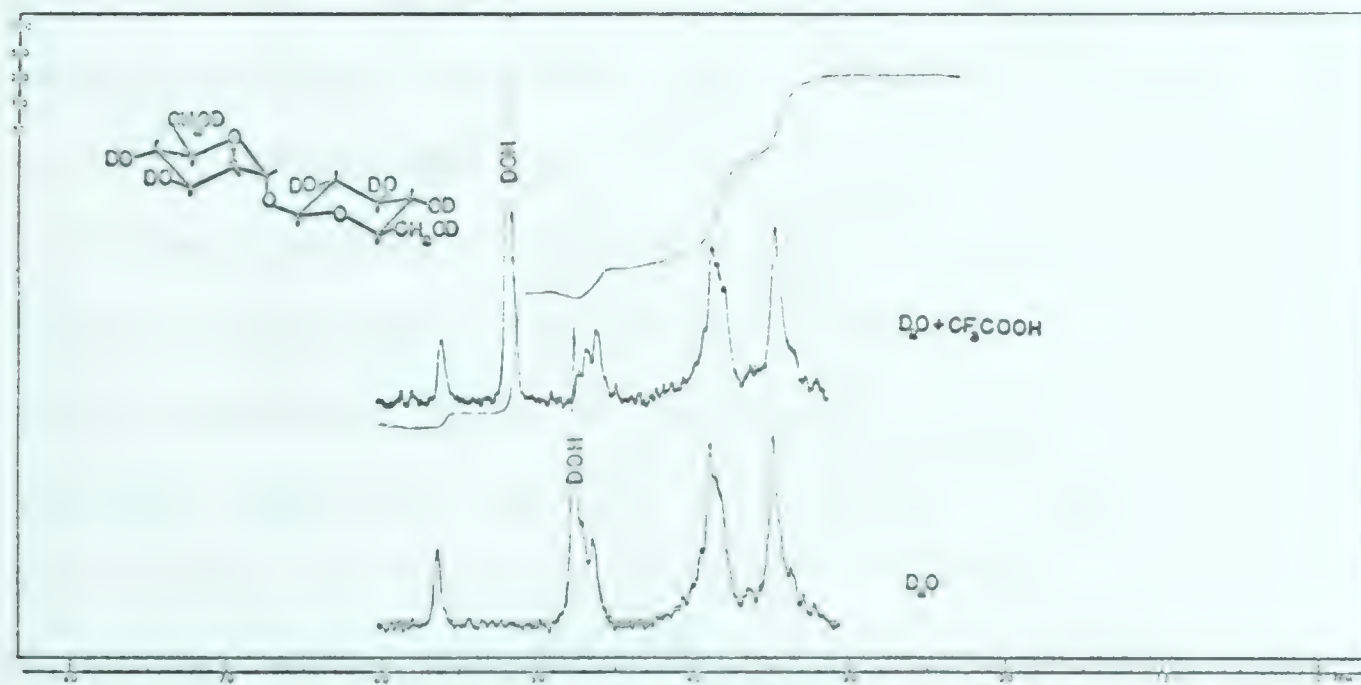


Fig. 5. β -D-Glucopyranosyl 2-Deoxy-2-iodo- α -mannopyranoside (12) (Deuterium Oxide and Trifluoroacetic Acid).

was in fact established by the n.m.r. spectrum of the product of hydrogenolysis as indicated a little later. The anomeric hydrogen of the β -D-glucopyranosyl moiety is partly hidden under the deuterium hydroxide peak at 5.23τ . Attempts to shift the deuterium hydroxide peak by the addition of one drop of 10 M sodium deuter-oxide resulted in extensive degradation. The solution assumed a yellow color. The signal at 4.35τ had disappeared in the time taken to scan the spectrum. On adding nitric acid to the yellow solution it turned colorless, and addition of aqueous silver nitrate gave a yellow precipitate of silver iodide. The decomposition is most probably due to the 2,3-trans-elimination of hydrogen iodide from 12 catalysed by the strong base. Trifluoroacetic acid was successful in displacing the deuterium hydroxide peak, Fig. 5, without hydrolysing the glycosidic linkage too quickly. Integration showed that the signals for two protons were underneath the deuterium oxide peak, and the rest of the spectrum integrated for 11 protons. The anomeric proton of the β -D-glucopyranosyl moiety was not readily observed in the presence of the other ring proton. The bromine analog (16) of 12, gave a spectrum, Fig. 9, which was almost identical but for minor chemical shifts. For the bromo compound (16), a typical spacing for diaxial coupling of protons was observed of 8 c.p.s. at 5.52τ , (Fig. 10), after the addition of pyridine and it was assigned to the β -D-glucopyranosyl residue.

Compound 12 was hydrogenolysed with palladium on charcoal as the catalyst, and acetylation of the product yielded the crystalline heptaacetate, 13. Final proof of the structure of 12 was

obtained by interpretation of the n.m.r. spectra of compound 13 and of the product formed on deacetylation of 13, which are given in Figs. 6 and 7, respectively. In the case of compound 13, the signals from 4.5τ to 5.5τ have the intensity of 7 protons and are assigned to the 5 pyranose-ring protons on carbons bearing acetoxy groups together with the two anomeric protons. The signals from 5.5τ to 6.5τ correspond to 6 protons and are assigned to the carbon-5 and carbon-6 protons in both rings. The twenty one acetyl-group protons and the two methylene-group protons are expected to have their signals in the region 7.5τ to 8.5τ . Integration indicated twenty three protons in this region as expected for the structure assigned to 13. The deacetylated product of 13 was not obtained in a crystalline condition but the n.m.r. spectrum of the syrup, Fig. 7, is that expected for 2-deoxy- α -D-glucopyranosyl β -D-glucopyranoside. The doublet of intensity one at 5.3τ with a spacing 7 c.p.s. is readily assigned to the anomeric proton in the β -D-glucopyranosyl moiety. The position and structure of the signal at 4.6τ with an intensity corresponding to one proton is that expected for the anomeric proton of a 2-deoxy- α -D-glucopyranoside (44). Lemieux and Levine (44) also could not resolve the quartet expected from weak coupling of the anomeric proton with the two protons on carbon-2. For the β -D-isomers well resolved quartets were obtained. As expected the signals from 5.7τ to 7τ integrated for 11 protons and those from 7.3τ to 8.7τ for two protons, readily assigned to the methylene group. A first order analysis of the methylene group was not possible.

As expected the deacetylated product was rapidly hydrolysed

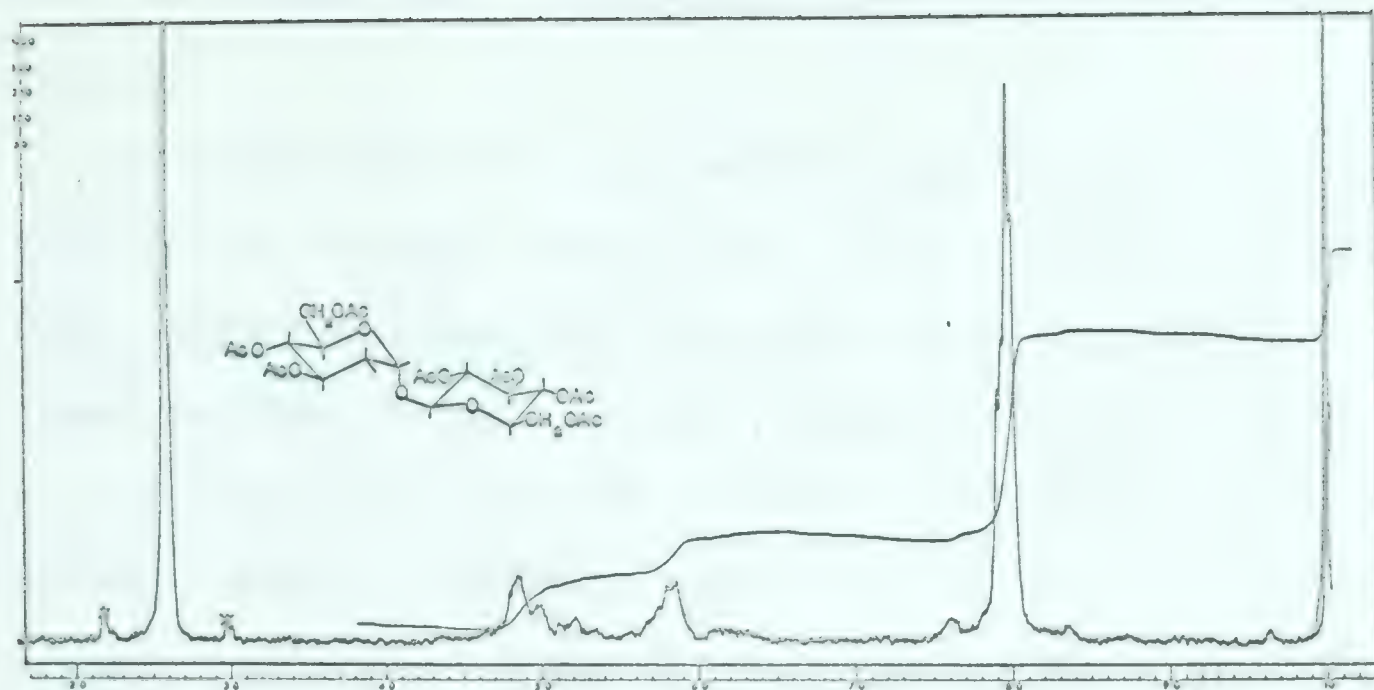


Fig. 6. 2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl 2-Deoxy-3,4,6-tri-O-acetyl-α-D-glucopyranoside (13) (Chloroform).

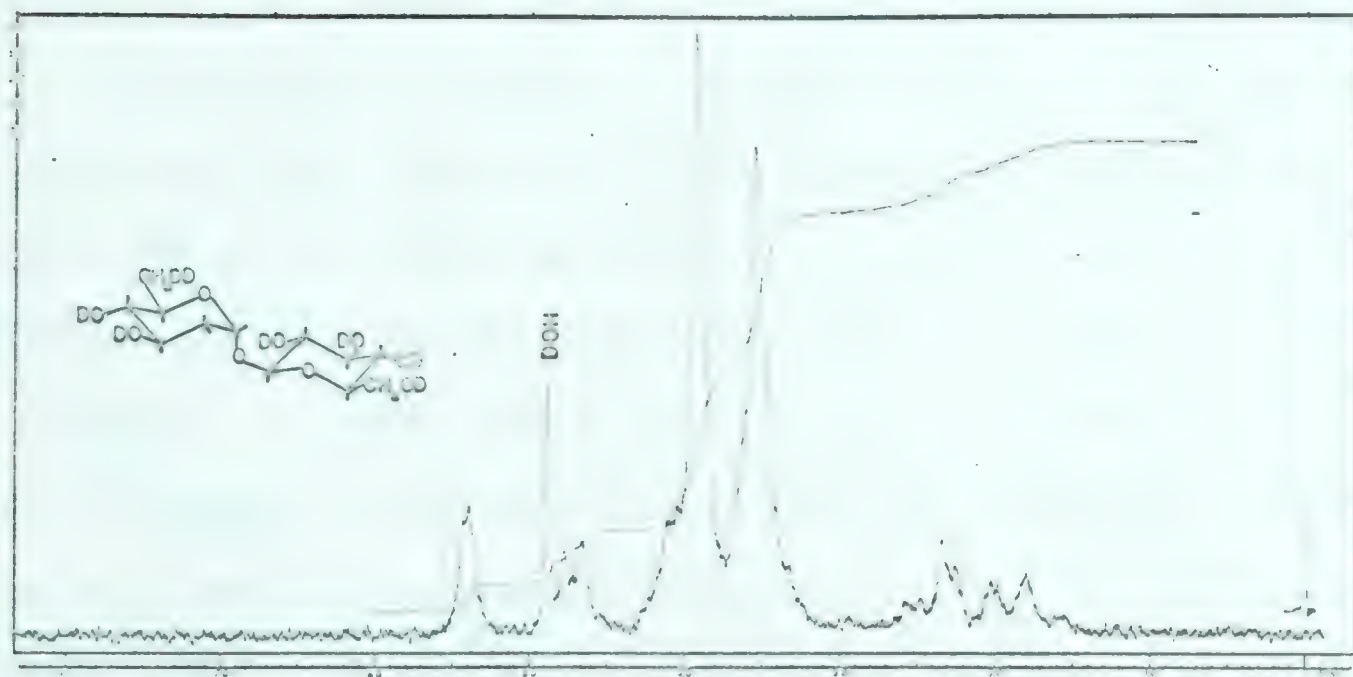


Fig. 7. β-D-Glucopyranosyl 2-Deoxy-α-D-glucopyranoside (Deuterium Oxide).

by dilute hydrochloric acid (typical of 2-deoxyglycosides), to give D-glucose and 2-deoxy-D-glucose as shown by paper chromatography.

The modified Prevost reaction was extended to the preparation of the bromine analog (16) of the 2-deoxy-2-iododisaccharide (12). Its structure (16) was deduced from the n.m.r. spectra shown in Figs. 9 and 10. The signal at 4.43τ is readily assigned to the anomeric proton of the 2-bromo-2-deoxy- α -D-mannopyranosyl moiety. When pyridine is added to shift the deuterium hydroxide signal, the above signal is now found at 4.7τ and a doublet of spacing 8 c.p.s. at 5.52τ is revealed, although partly obscured by another signal. Nevertheless, the signal can be safely assigned to the anomeric proton in the β -glucopyranosyl moiety. The confirmation of the structure was completed by reduction and acetylation to the 2-deoxy-neo-D-trehalose heptaacetate (13).

The molar rotations of compounds 12 and 16 and of related glucosides are reported in Table III. Following Brewster's approach to the rationalization of optical rotations (83), the difference in rotation between I and II is described by,

$$2k(\text{O-H})^2 + k(\text{I-H})(\text{O-H}) + \text{P}(\text{C}_2\text{I})^* = 342 - 165 = 177$$

Compounds III and IV differ in configuration in the same way as do I and II and their rotations differ to about the same extent (158°). Thus the configuration assigned to 12 is confirmed.

* Brewster has no notation for the permolecular screw pattern but he assigns the empirical value of 60° for an axial hydroxy group at C_2 or C_4 in the tetrahydropyran ring (Reference (83), p.5492). Therefore the notation $\text{P}(\text{C}_2\text{I})$ is intended to signify the absolute value of the permolecular contribution due to axial iodine at C_2 .

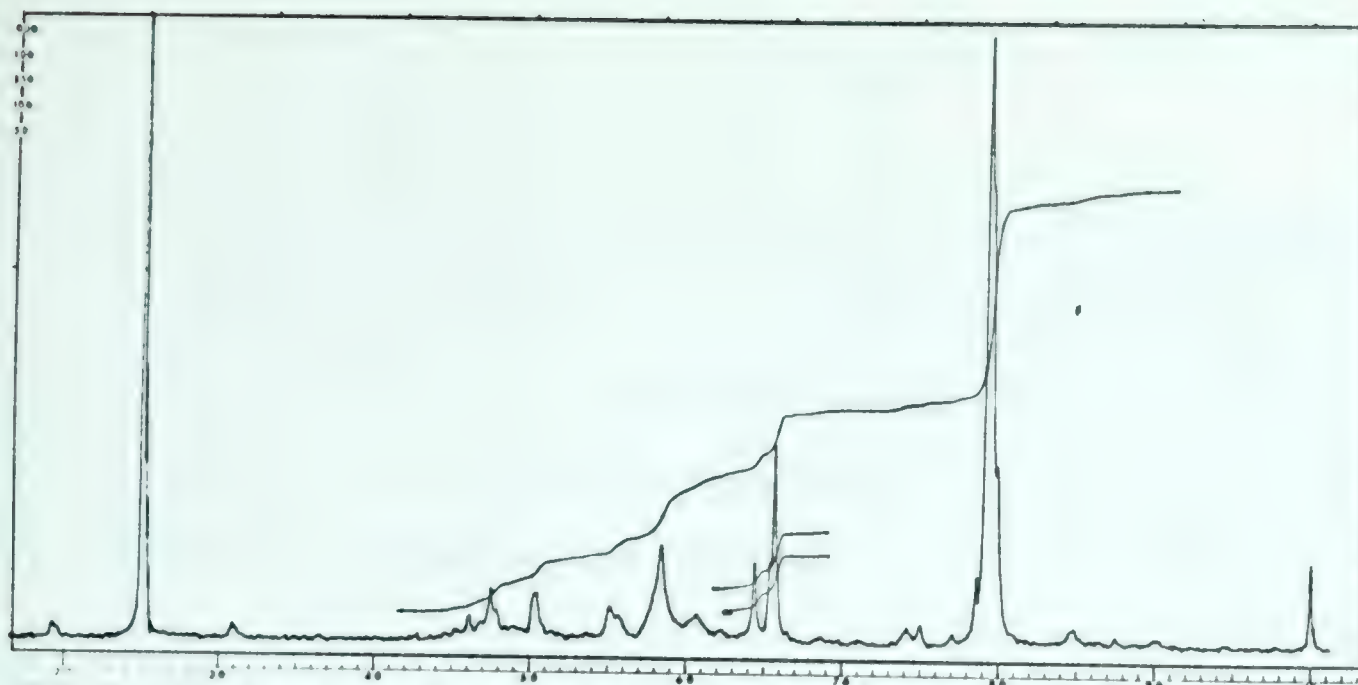


Fig. 8. Methyl 3,4,6-Tri-O-acetyl-2-bromo-2-deoxy- α -D-mannopyranoside (14) and the Corresponding β -Glucoside (15) with a Trace of another component (Chloroform).

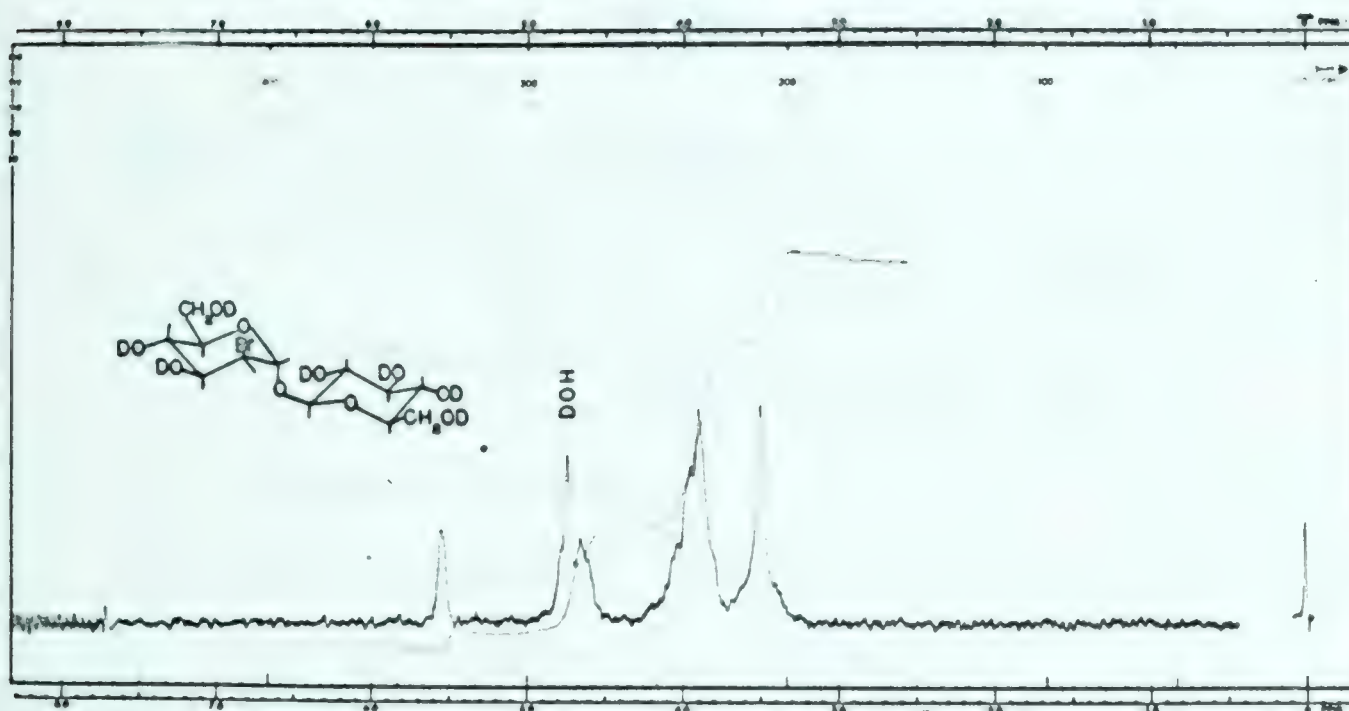


Fig. 9. β -D-Glucopyranosyl 2-Bromo-2-deoxy- α -D-mannopyranoside (16) (Deuterium Oxide).

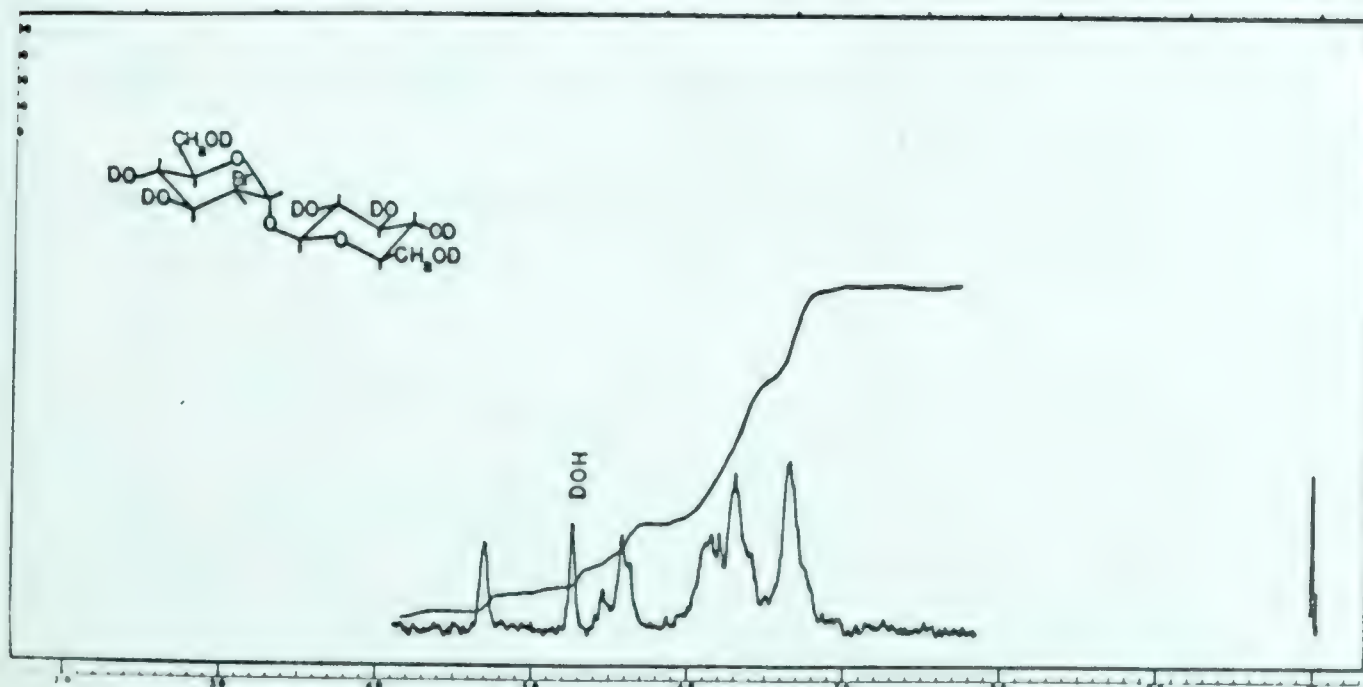


Fig. 10. β -D-Glucopyranosyl 2-Bromo-2-deoxy- α -D-mannopyranoside (16) (Deuterium Oxide and Pyridine).

An alternative argument in favour of the configuration for 12 is to note that addition of the difference (158°) in the rotations of compounds III and IV to the rotation of II (165°) gives a value (323°) in much closer agreement with the molar rotation of D-neotrehalose (342°) than with that either of D-isotrehalose (-133°) or D-trehalose (675°).

TABLE III
OPTICAL ROTATION OF GLYCOSIDES

No.	Compound	Molar Rotation	Reference
I	D-Neotrehalose (β -D-glucopyranosyl α -D-glucopyranoside)	342	(31)
II	β -D-Glucopyranosyl 2-deoxy-2-iodo- α -D-mannopyranoside (<u>12</u>)	165	
III	Methyl α -D-glucopyranoside	308	(84)
IV	Methyl 2-deoxy-2-iodo- α -D-mannopyranoside	150	(44)
V	Methyl β -D-glucopyranoside	-66	(84)
VI	Methyl 2-deoxy-2-iodo- β -D-glucopyranoside	21	(44)
VII	D-Isotrehalose (β -D-glucopyranosyl β -D-glucopyranoside)	-133	(31)
VIII	D-Trehalose (α -D-glucopyranosyl α -D-glucopyranoside)	675	(33)
IX	β -D-Glucopyranosyl 2-bromo-2-deoxy- α -D-mannopyranoside (<u>16</u>)	160	

It is of interest to note that, according to Brewster's rules (83), the bromine analog (16) of 12 would be expected to have a greater dextrorotation than 12. This would follow from the lower rotational rank of bromine as compared to iodine. That is, the terms $k(\text{Br-H})(\text{O-H})$ and $P(\text{C}_2\text{Br})$ are expected to be less than the

corresponding terms with iodine. In fact the molar rotation of 16 was slightly less than that of 12. Caution must therefore be exercised in extending Brewster's rules to screw patterns involving atoms of high rotational rank. A further indication of caution in this regard is found in the rotations for compounds V and VI. Following Brewster's rules these compounds should have the same rotation. It is seen however that their molar rotations differ by 87° .

In preliminary experiments, when Celite chromatography (66) was used to isolate the deacetylated 2-deoxy-2-halogenodisaccharides, no crystalline material with the 2-deoxy-2-iodo- β -D-glucopyranoside configuration could be obtained. Also paper chromatograms were negative regarding the evidence of the formation of any other stereoisomers than the 2-deoxy-2-iodo- α -D-manno isomer. On the other hand both the 2-deoxy-2-iodo and 2-bromo-2-deoxydisaccharides (12) and (16) crystallized extremely slowly and incompletely from the crude syrup, possibly suggesting an impurity. Only trace amounts of glucose could be detected chromatographically as an impurity of the crude syrup.

In attempting to extend the above modified Prevost reaction to the formation of the α,α -linked trehalose analog, it was necessary to prepare 2,3,4,6-tetra-O-acetyl- α -D-glucose.

Schlubach and Wolf (85) reacted 2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl chloride with silver carborate in either ether or acetone containing a little water to obtain a product melting at $107-108^\circ$, $[\alpha]_D + 138.9^\circ$, (c, 0.9 in chloroform). The compound was assigned the structure of 2,3,4,6-tetra-O-acetyl- α -D-glucose.

The product we obtained on using this procedure failed to crystallize.

Georg (86) treated α -acetobromoglucose with silver nitrate in ether containing a little water. He isolated material of m.p. 99-100°, $[\alpha]_D + 135^\circ$ (c, 4 in chloroform), and claimed its structure to be 2,3,4,6-tetra-O-acetyl- α -D-glucose. The mechanism for its formation was postulated as Walden inversion at the anomeric center of α -acetobromoglucose with replacement of bromide by the nitrate, followed by a second Walden inversion as water attacks the β -nitrate. Georg could not raise the melting point of his product to that of Schlubach and Wolf's material in spite of repeated recrystallization from ether-petroleum ether. Georg obtained a sample of Schlubach's material and on recrystallization from ether-petroleum ether the melting point fell to 98-99°, but when he recrystallized the compound from ether alone, the melting point rose immediately to 112-113°. He then obtained the same result with his own sample. Georg therefore concluded that dimorphic forms had been obtained.

Lemieux and Brice (67) treated tetra-O-acetyl- β -D-glucopyranosyl chloride with silver acetate in 90% aqueous acetic acid. They isolated crystals of m.p. 96-98°, $[\alpha]_D + 138^\circ$ (c, 0.44 in chloroform). The good agreement with Georg's values led them to assume they had prepared the 2,3,4,6-tetra-O-acetyl- α -D-glucose.

We repeated Lemieux and Brice's directions to obtain a product of m.p. 110-111°, $[\alpha]_D + 149^\circ$ (c, 1 in chloroform), and the n.m.r. spectrum shown in Fig. 11. The compound (40% yield) was crystallized from ether-Skellysolve B. In repeating this experi-

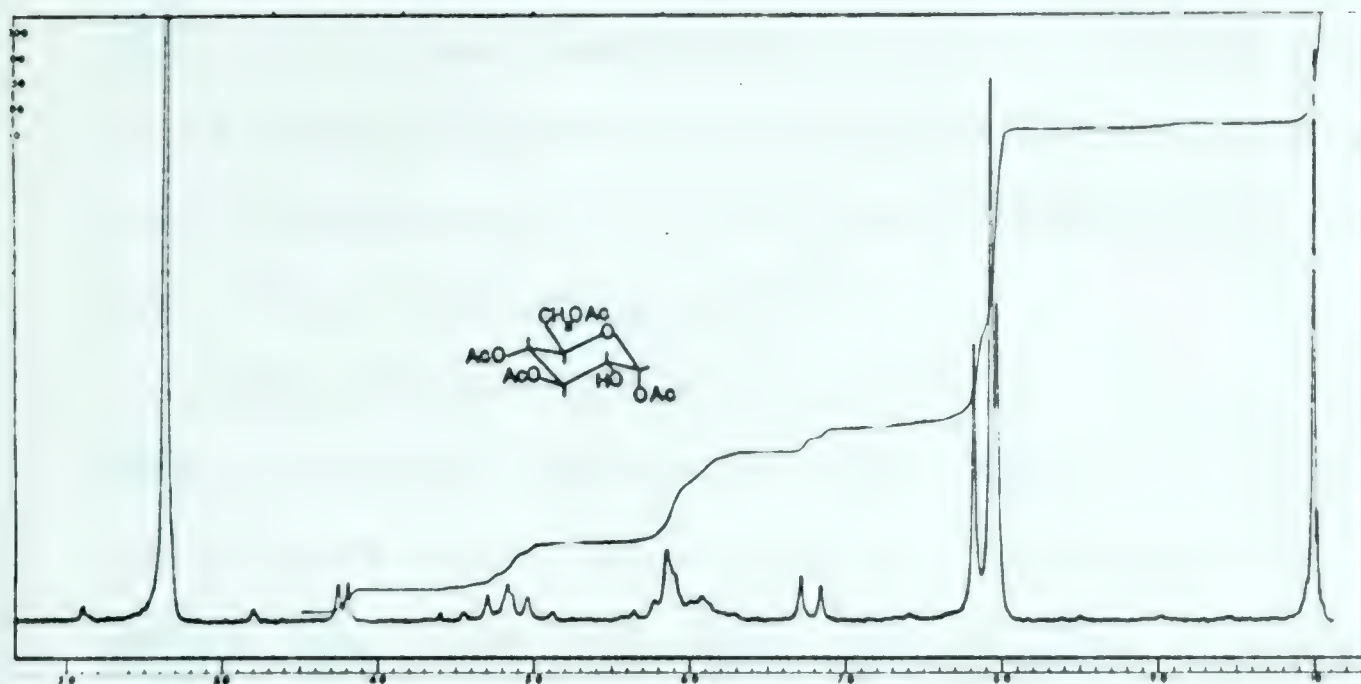


Fig. 11. 1,3,4,6-Tetra-O-acetyl- α -D-glucopyranose (17)
(Chloroform).

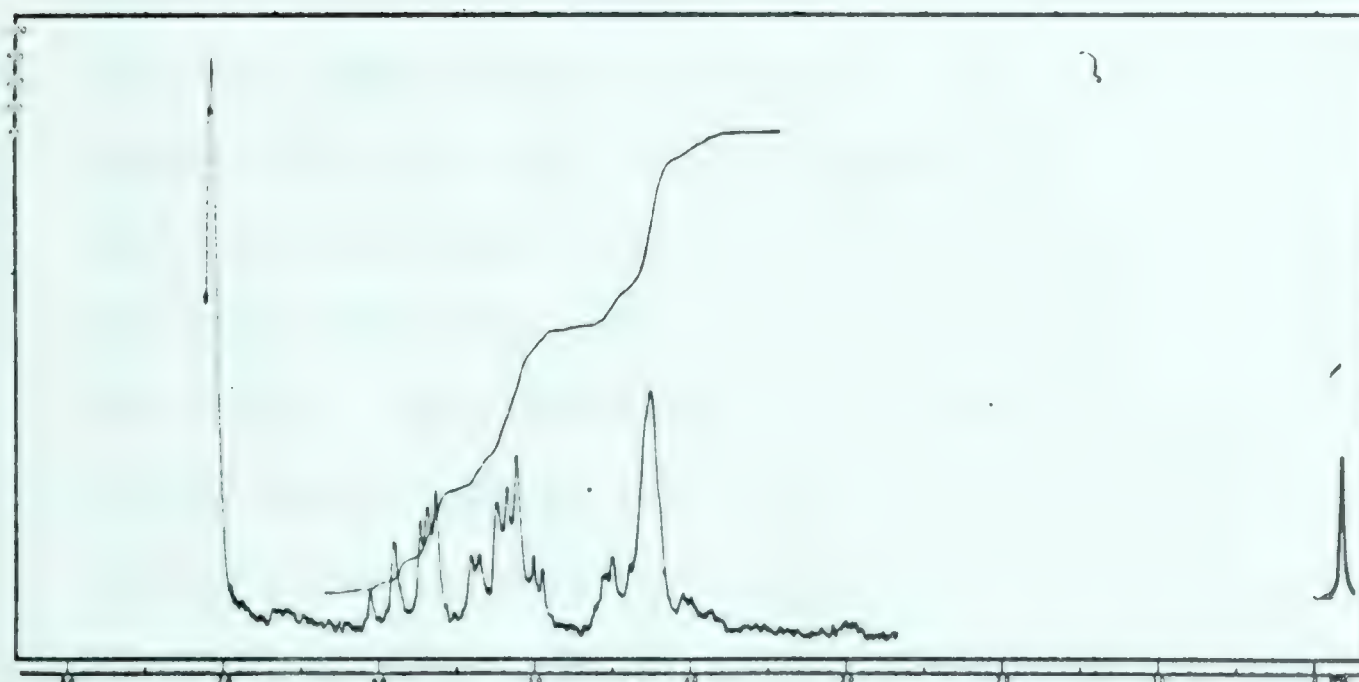


Fig. 12. The Equilibrium Mixture after the Mutarotation of
2,3,4,6-Tetra-O-acetyl- β -D-glucopyranose in Pyridine
(Pyridine).

ment on a larger scale, material of m.p. 90-95° was obtained from ether-Skellysolve B, but with the same n.m.r. spectrum as shown in Fig. 11. It was possible to raise the melting point to 110-111° on recrystallization and seeding with the crystals of m.p. 110-111°. A mixture of the two crystalline samples, m.p. 110-111° and m.p. 90-95°, melted at 106-109°.

The structure indicated by the n.m.r. spectrum in Fig. 11, is clearly that of 1,3,4,6-tetra-O-acetyl- α -D-glucopyranose. The spacing of 3.75 c.p.s. of the anomeric proton at 3.77 τ is that of a gauche pair of protons (87), and therefore the anomeric configuration is α . The chemical shift is much too far to low field for a free hydroxyl at the anomeric center but is typical of a 1-O-acetate (88). α -Glucopyranose pentaacetate has its anomeric signal at 3.63 τ , spacing 3.5 c.p.s. The acetate signal shifted downfield to 7.82 τ is characteristic of axial acetoxy groups (88). The only other signal amenable to first order analysis is the doublet at 6.77 τ and with a spacing of 7.5 c.p.s. which is assigned to the hydroxyl proton since the signal was not present in the spectrum after the chloroform solution had been shaken with deuterium oxide. The coupling of the hydroxyl proton with the carbon-2 proton was not always observed and the doublet has appeared as a singlet, due to rapid exchange, and sometimes it was not readily observed at all. The 2-proton is shifted to relatively high field (as determined by the intensities) from the 3- and 4- protons. This is normally observed when the deshielding of the acetoxy group is removed (88).

Lemieux and Huber (89) prepared 1,3,4,6-tetra-O-acetyl- α -D-

glucose by an unequivocal route from 3,4,6-tri-O-acetyl- β -D-glucopyranosyl chloride and silver acetate in acetic acid. The properties of the tetraacetate were reported as m.p. 97-98°, $[\alpha]_D + 145^\circ$ (chloroform). Matsuda (90) prepared 1,3,4,6-tetra-O-acetyl- α -D-glucose by a similar method using mercuric acetate instead of silver acetate. His material melted at 98-100°, $[\alpha]_D + 143^\circ$ (c, 3 in chloroform). Recently, Helferich and Zirner (91) also prepared 1,3,4,6-tetra-O-acetyl- α -D-glucose by a new route. They acetylated glucose in acetic anhydride and perchloric acid solution, and then to the cooled solution added phosphorous tribromide followed by water. After 1.5 hours at room temperature aqueous sodium acetate solution was slowly added at 10°. The product was isolated by extraction with chloroform, and it had a m.p. 98-100°, $[\alpha]_D + 141.1^\circ$ (c, 3.2 in chloroform). The proof of the structure consisted in forming the 2-O-mesyl derivative which was then treated with hydrogen bromide to introduce bromine at the anomeric center. The mesyl group was still retained in the molecule and must therefore be at the 2- position. It showed a depression of melting point with Georg's material. The product we obtained by Lemieux and Brice's method and which undoubtedly was 1,3,4,6-tetra-O-acetyl- α -D-glucose is so similar in its properties to the materials reported by Georg, and Schlubach and Wolf, especially in its dimorphic nature, that it can be safely concluded that in fact they had prepared the 1,3,4,6-tetraacetate. In the light of the very facile 1,2-acetyl migration of the 1,3,4,6-tetraacetate (see below), the reducing properties of Georg's and Schlubach and Wolf's material should not be regarded as evidence

for the 2,3,4,6-tetraacetate. The only evidence to support this structure is the depression of melting point on admixture of Helferich's 1,3,4,6-tetraacetate with Georg's "2,3,4,6-tetraacetate". This may have been fortuitous.

The mechanistic interpretation of the formation of 1,3,4,6-tetra-O-acetyl- α -D-glucose from 2,3,4,6-tetra-O-acetyl- β -D-glucosyl chloride is most readily understood in terms of neighboring group participation.

Since in Schlubach and Wolf's and Georg's preparations either ether or acetone was used as solvent, the 1-O-acetyl-group in the product must have been at the 2-position in the reactant. Presumably an intermediate 1,2-acetoxonium ion is formed which reacts with water to form the transient acid orthoester, which can then rearrange to either the 1,3,4,6- or 2,3,4,6-tetra-O-acetyl- α -D-glucose. Our results indicate that in the glucose series at any rate the major first product is the 1,3,4,6-tetraacetate. That 1,3,4,6-tetra-O-acetyl- α -D-glucose in aqueous solution is thermodynamically less stable than the 2,3,4,6-isomer was established as follows. Although the 1,3,4,6-tetraacetate (17) did not mutarotate in dry pyridine, the specific rotation of an aqueous solution, as would now be expected from the earlier published data, changed from 147.5° to 71° in 12 hours. That the product consisted essentially of 2,3,4,6-tetra-O-acetyl- α - and β -D-glucose in about equal amounts was evident from the n.m.r. spectrum in chloroform. No trace of the axial 1-O-acetyl signal at 7.82τ and characteristic of the 1,3,4,6-tetraacetate (17) was present. The equilibrium mixture obtained on mutarotating 2,3,4,6-tetra-O-acetyl- β -D-glucose

in water had the same spectrum and rotation. That the mutarotation was due to acetyl group migration followed by $\alpha \rightleftharpoons \beta$ interconversion was evident since the intensity of the signals for acetyl groups required the product to be a mixture of tetraacetates.

It was found that on equilibrating a solution of 2,3,4,6-tetra-O-acetyl- β -D-glucose in pyridine, the product contained 77% of the α -anomer. Lemieux (18) has pointed out the unexpectedly high percentage of the β -anomer of D-glucose in the equilibrium mixture in water is probably due to hydrogen bonding. Also the anomeric effect may be expected to decrease in polar solvents. It is therefore not surprising that a high proportion of the α -anomer exists in pyridine as is confirmed by the n.m.r. spectrum in Fig. 12.

Equatorial protons are generally found to lower field than axial protons in an otherwise similar environment (88). Also oxygen in a 1,3-diaxial relationship to hydrogen deshields the signal in the n.m.r. spectrum for that hydrogen. Thus the protons at 3.92 τ , triplet with spacing 9.5 c.p.s. and at 4.16 τ , doublet with spacing 3 c.p.s. are readily assigned to the protons on carbon-3 and -1, respectively, of α -D-glucose tetraacetate. The integrated intensities of these hydrogens corresponded to 77% of the α -anomer and this was confirmed by acetylation and benzoylation of the mixture, to give α -D-glucopyranose pentaacetate and 2,3,4,6-tetra-O-acetyl-1-O-benzoyl- α -D-glucopyranose, respectively. The n.m.r. spectrum of the crude benzoylated product had the signal for the anomeric proton at 3.42 τ , spacing 3.5 c.p.s. As is normally observed for benzoylated sugars, the signal was to lower field than that for the anomeric proton of α -glu-

cose pentaacetate, anomeric signal at 3.63 τ , spacing 3.5 c.p.s. From the integrated intensities 80% of the product was the α -anomer. The isomerization of the 1,3,4,6-tetraacetate of α -D-glucose in aqueous solution was independently established by Helferich and Zirner (91) during the course of this investigation.

When the syrup containing 77% of the α -anomer of D-glucose 2,3,4,6-tetraacetate was used as the "alcohol" in the modified Prevost reaction in the expectation of forming an α,α -linked analog of trehalose, only the α,β -linked isomer (12) was obtained. The yield was about the same as when pure 2,3,4,6-tetra-O-acetyl- β -D-glucose was used as the "alcohol". Presumably mutarotation took place more rapidly than did the reaction of the α -anomer, and the α -anomer reacted only very slowly as compared to the β -anomer.

With regard to the formation of 1,3,4,6-tetra-O-acetyl- α -D-glucose, it is of interest to note that Perlin (54) found the acid hydrolysis of the diastereoisomeric β -D-mannose 1,2-(benzyl orthoacetates) yielded 2-O-acetyl-D-mannose. Evidently, the configuration is important in determining whether the acetyl group materializes at the 1- or the 2-position. Ness and Fletcher (92) showed 1,3,5-tri-O-benzoyl- α -D-ribose is formed on the acid hydrolysis of tri-O-benzoyl-D-ribofuranosyl bromide. Since the hydrogenolysis of α -D-ribose 1,2-(benzyl orthobenzoate)-3,4-di-O-benzoate also yielded 1,3,5-tri-O-benzoyl- α -D-ribose, the cyclic orthoacid intermediate must be unstable and rearranges to the 1-O-benzoyl product. The 1-O-benzoyl group was found to migrate to the 2-position in alkaline solution. These results nicely corroborate our observations. The isolation by Antia (93) of 1,3,4-

tri-O-acetyl- α -D-xylose as a product of the reaction of tri-O-acetyl- α -D-xylopyranosyl bromide in aqueous acetone and in the presence of silver carbonate is noteworthy. Most likely, the reaction involved anomerization of the α -bromide by attack of liberated bromide ion.

B. THE PREPARATION OF N-GLYCOSIDES

It was thought necessary to use s-collidine complexes of the halonium ion to avoid nucleophilic competition of the base with the alcohol in the preparations of 2-deoxy-2-halogenoglycosides reported in Section B of the Experimental. Since iodonium dipyridine perchlorate (6) is readily prepared, it was of interest to determine how quickly the pyridine would attack the iodonium π -complex. A rapid reaction took place with D-glucal triacetate to form acetylated N-(2-deoxy-2-iodo-glycosyl)-pyridinium perchlorates. The halonium dipyridine complexes were thus unsuitable for the synthesis of O-glycosides, but they were useful reagents in the preparation of new types of nucleosides. The reaction led to the formation of two crystalline products, 18 and 19, obtained in 70% and 30% yields respectively.

The n.m.r. spectra, Figs. 13 and 14, of 18 and 19 provided signals for the anomeric protons as doublets at 3.30τ and 3.26τ respectively (94). Unexpectedly the 1- and 2-protons were coupled to an extent of 9-10 c.p.s. for both of these compounds. The magnitude of these coupling constants indicates that for both compounds the 1- and 2-protons are in axial orientation. This relationship is expected for the β -gluco-configuration but unex-

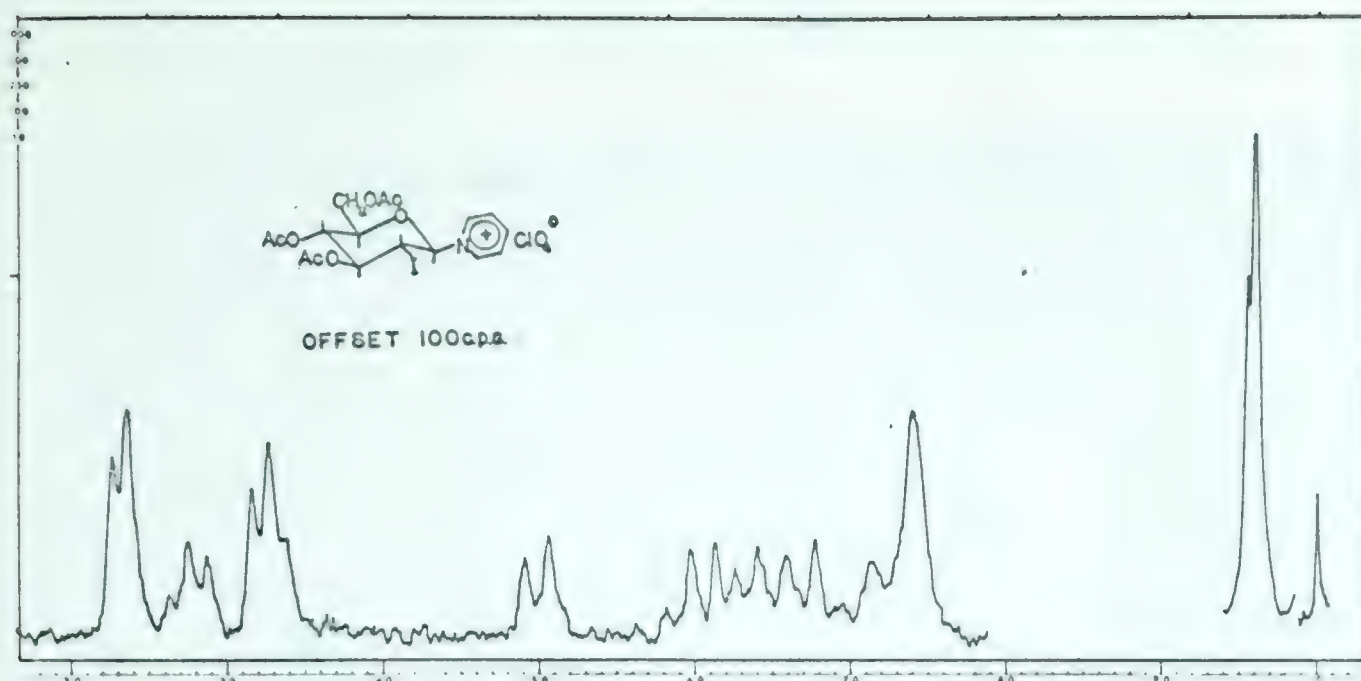


Fig. 13. N-(3,4,6-Tri-O-acetyl-2-deoxy-2-iodo-β-D-glucopyranosyl)-pyridinium Perchlorate (18) (DMSO). (Solvent signals omitted).

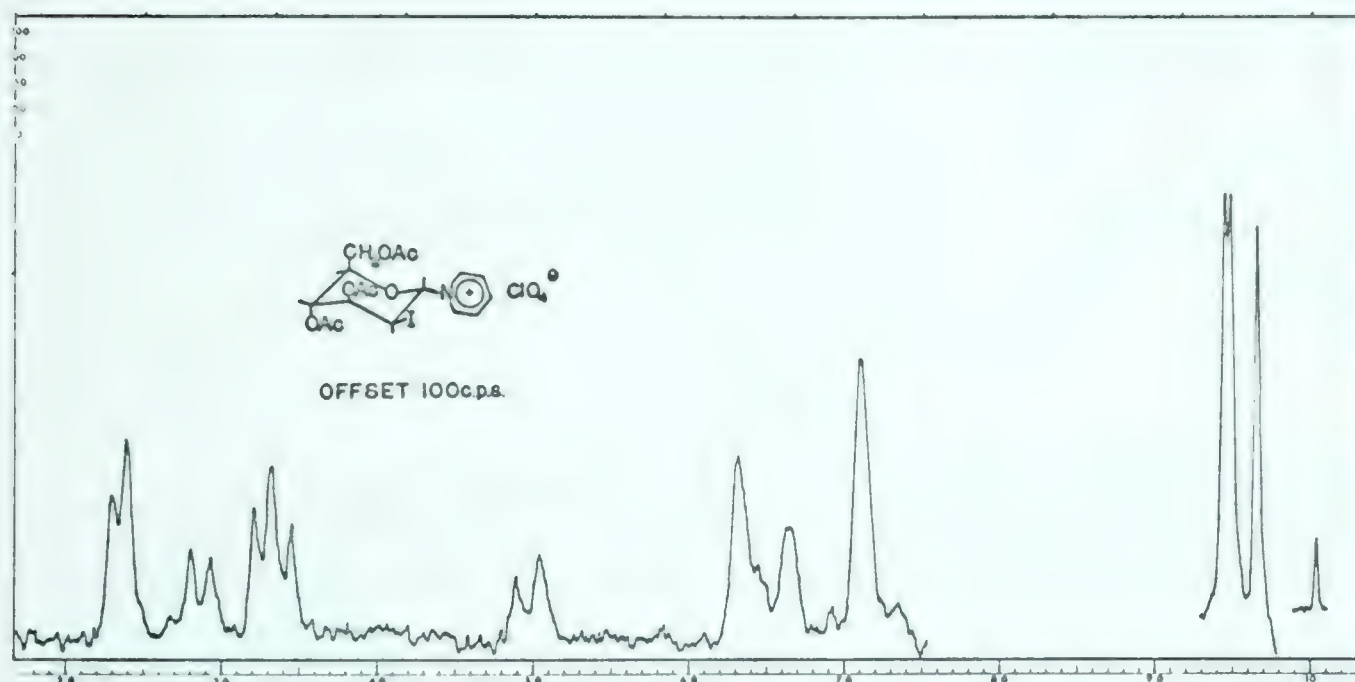


Fig. 14. N-(3,4,6-Tri-O-acetyl-2-deoxy-2-iodo-α-D-mannopyranosyl)-pyridinium Perchlorate (19) (DMSO). (Solvent signals omitted).

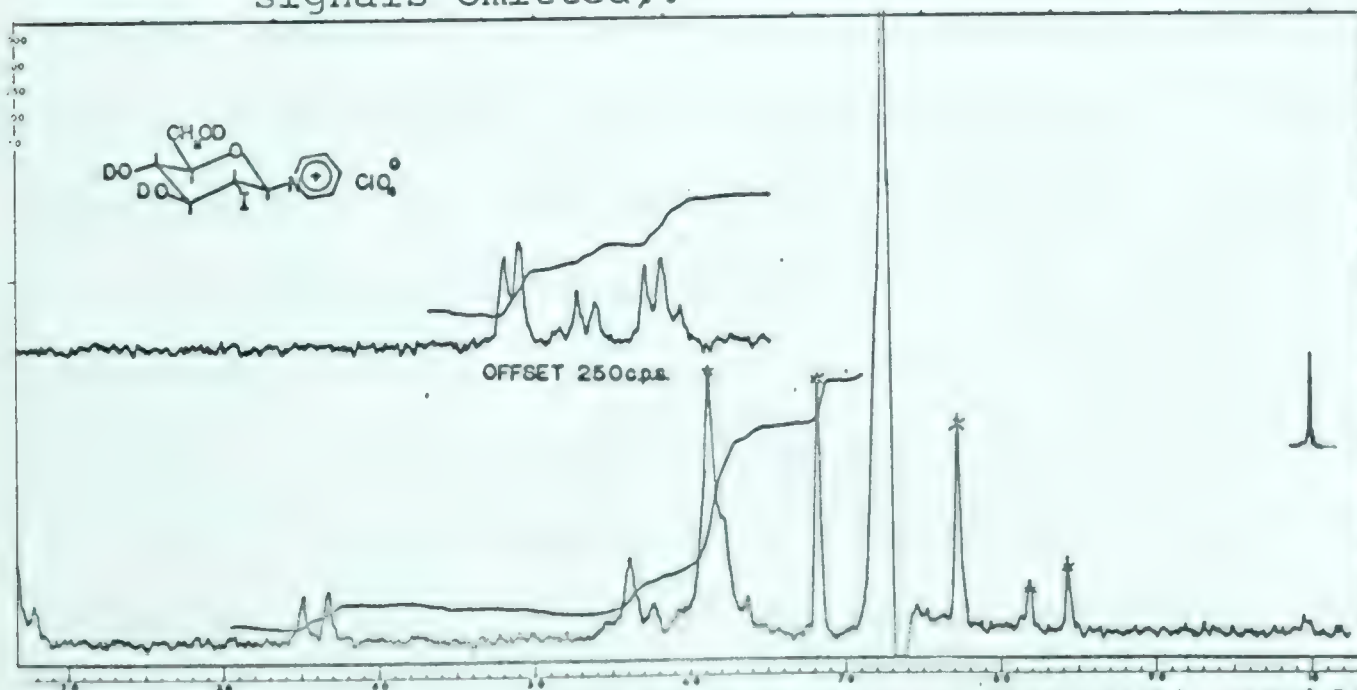
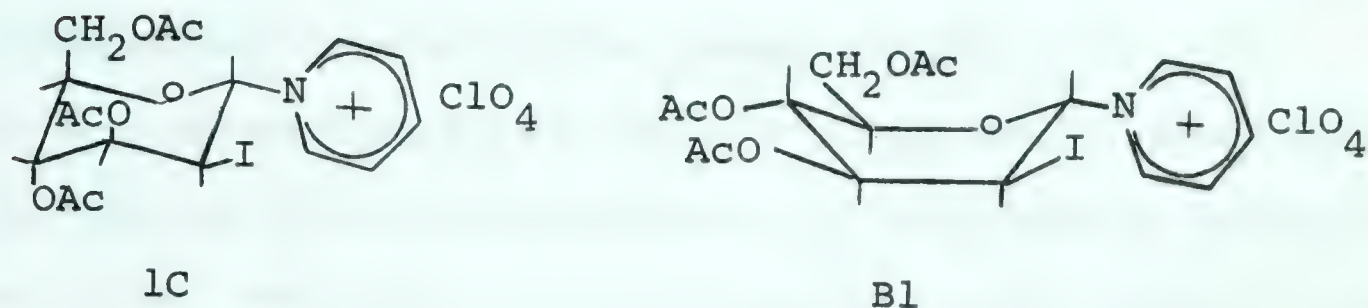


Fig. 15. N-(2-Deoxy-2-iodo-β-D-glucopyranosyl)-pyridinium Perchlorate (20) (DMSO).

pected for the α -manno-configuration unless the compound exists in the 1C conformation or the B1 conformation, as shown in Diag. 4 (95).



Diag. 4

The isomer (19) formed in 30% yield was assigned the α -manno-configuration since it was much less stable than the other product (18) of the reaction. Thus, whereas 19 was immediately decomposed to D-glucal triacetate and iodine as a suspension in aqueous potassium iodide solution dissolved, the isomer 18 showed no reaction under similar conditions over 24 hours. Also 19 isomerized to 18 when dissolved in pyridine. These properties are obviously in keeping with the strained structure for 19 as evidenced by the n.m.r. spectral data. It seems highly unlikely that the 1- and 2-protons of 19 could be coupled to an extent of at least 9 c.p.s. because of eclipsing since this would require eclipsing of the iodine and the pyridinium group. Also the reaction must be expected to give the 1,2-trans- adduct. There-

fore we concluded that the isomer (19) does possess the α -manno-configuration and exists in a conformation approaching either the 1C or B1 conformations. The 1C conformation is suggested by the fact that the n.m.r. signals for two of its acetyl groups are at substantially lower field (10-15 c.p.s.) in a variety of solvents (DMSO, methylene chloride, acetone, pyridine and methanol) than the corresponding signals in the isomer 18 (88).

Further chemical characterization of 18 was obtained by its reduction to the 1,4-dihydropyridine (21) with sodium dithionite. Compound 21 was unstable in chloroform and carbon tetrachloride, and iodine was rapidly released. Nevertheless the n.m.r. spectrum of the compound could be measured before decomposition was extensive and the spectrum closely resembled that of the known 1,4-dihydropyridine (27).

Compound 18 was deacetylated in methanol and triethylamine. The structure of the crystalline product was confirmed by its n.m.r. spectrum in DMSO (Fig. 15). The relative intensities were in accord with expectation as was the chemical shift and spacing for the anomeric doublet, 3.58 τ , 9.5 c.p.s. The unstable 2-deoxy-2-iodo- α -D-manno compound (19) decomposed to dark materials under the same conditions for deacetylation of 18. Other standard methods also failed.

The insolubility in water of the perchlorates prepared by the action of halonium perchlorate complexes on D-glucal triacetate, made it desirable to form the bromides. Attempts at the metathesis of the anions by shaking with aqueous potassium bromide were unsuccessful.

In retrospect that 19 should not possess the C1 conformation is readily attributed to the anomeric effect acting in reverse. The stability of the axial orientation known as the anomeric effect (14,15) results from the partial negative charges on the oxygen in O-glycosides, or the halogen in acetohalogenosugars, at the anomeric center. With quaternary N-glycosides a full positive charge is formally located on the nitrogen, and the anomeric effect (one could call it an anti-anomeric effect) will be such as to favour the already sterically favoured equatorial orientation. In anticipation of a later part of the discussion, N-(2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl)-pyridinium bromide has the C1 conformation. Therefore it appears that the axial iodine in the α -manno-configuration of 19 sufficiently destabilizes this conformation to cause it to invert to the 1C conformation (or possibly B1 conformation) in spite of the large 1,3-diaxial interactions that result.

Reactions of D-glucal triacetate with the bromonium dipyridine perchlorate complex (9) provided a crystalline product which was assigned the structure of N-(tri-O-acetyl-2-bromo-2-deoxy- β -D-glucopyranosyl)-pyridinium perchlorate (22) on the basis of its n.m.r. spectrum which closely resembles that of the iodo-analog 18. Although the α -manno-isomer could not be crystallized, its formation was inferred from the close similarity of the n.m.r. spectrum of the residual syrup with that of the 2-iodo analog, 19 (Fig. 14). Also, as expected from the properties of the iodo-analog (19), when the syrup was dissolved in pyridine, a further crop of the β -gluco-isomer (22) was obtained and the n.m.r. spec-

trum of the residual syrup showed a decrease in the intensity for the acetyl group at 7.73τ characteristic of the α -D-manno-isomer of 22.

Although the iodonium and bromonium di-s-collidine perchlorate complexes appeared not to react rapidly with D-glucal triacetate, the complexes prepared from α -picoline reacted readily although slower than the complexes derived from pyridine. In both cases only the β -gluco-isomers were obtained crystalline. The n.m.r. spectra for the iodo-(23) and bromo-(24) α -picolinium compounds are reproduced in Figs. 17 and 18, respectively. The compounds 23 and 24 did not react readily with iodide to liberate iodine, thus confirming the assignment of the large coupling constants as resulting from diaxial coupling in the β -gluco-configuration.

In an effort to prepare N-(tri-O-acetyl-2-bromo-2-deoxy- β -D-mannopyranosyl)-pyridinium bromide, D-glucal triacetate was brominated (45) and the syrupy product was dissolved in pyridine. The product which readily crystallized proved to be N-(tri-O-acetyl-2-bromo-2-deoxy- β -D-glucopyranosyl)-pyridinium bromide (25). The configuration of the compound 25 was evident from a comparison of its n.m.r. spectrum (Fig. 19) with that (Fig. 16) of the corresponding perchlorate salt (22). The n.m.r. spectrum of the residual syrup (Fig. 20) showed no signal for anomeric protons other than a rough singlet at 3.27τ (external TMS). In view of the 3.0 c.p.s. spacing at 3.12τ observed for the doublet of the anomeric proton (Fig. 28a) of the nearly pure N-(tetra-O-acetyl- α -D-glucopyranosyl)-pyridinium bromide (33), the 10 c.p.s. spacing for the

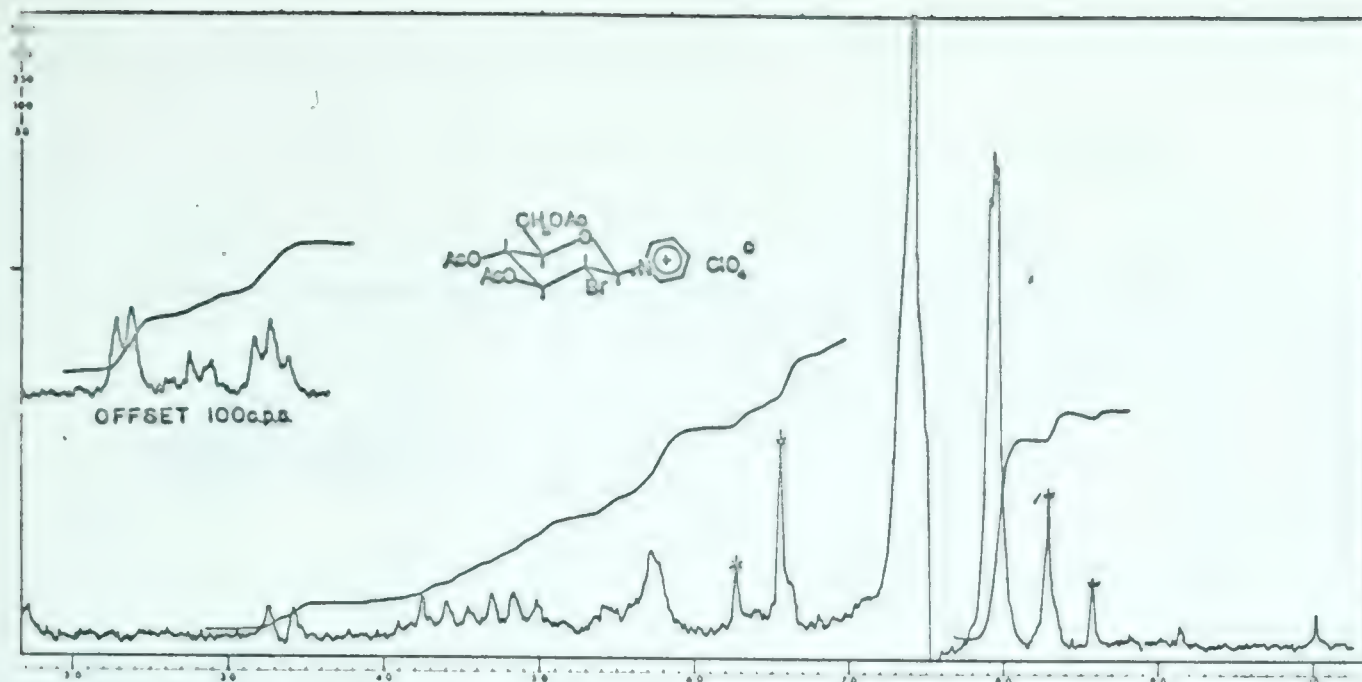


Fig. 16. N-(3,4,6-Tri-O-acetyl-2-bromo-2-deoxy-β-D-glucopyranosyl)-pyridinium Perchlorate (22) (DMSO).

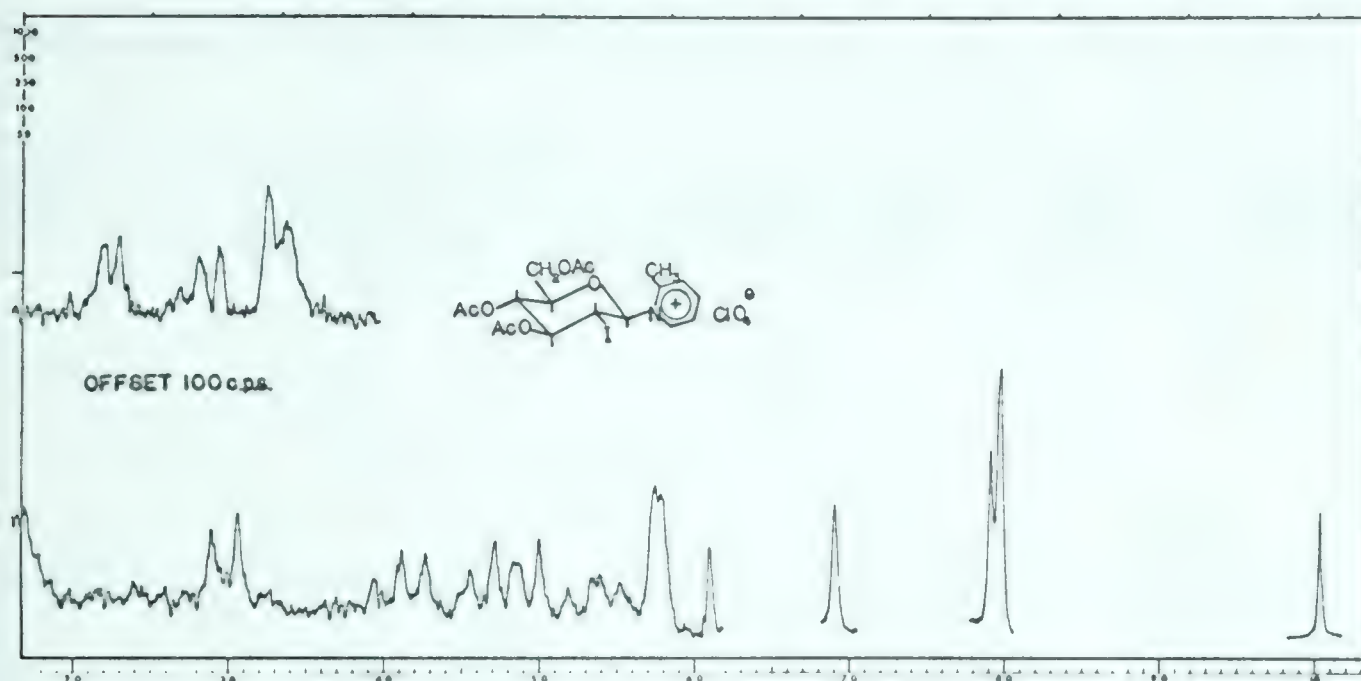


Fig. 17. N-(3,4,6-Tri-O-acetyl-2-deoxy-2-iodo-β-D-glucopyranosyl)-α-picolinium Perchlorate (23) (DMSO). (Solvent signals omitted and reduced amplitude above 6.5 τ).

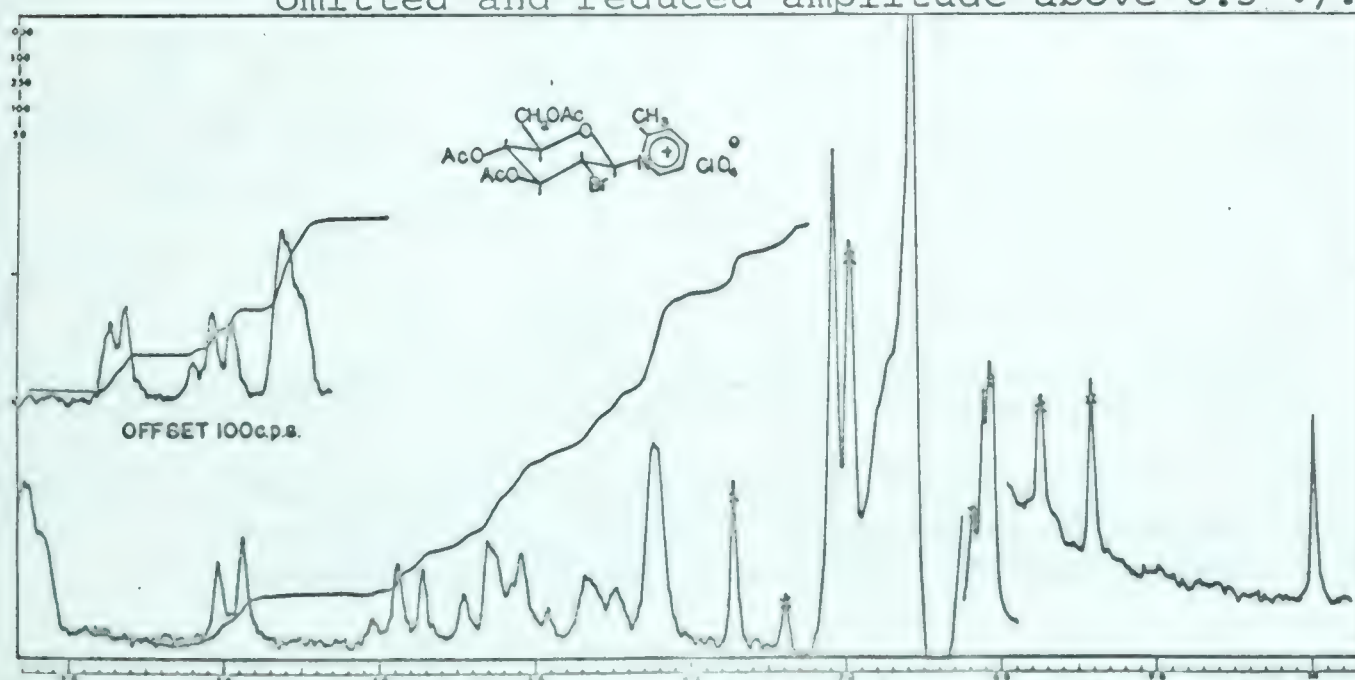


Fig. 18. N-(3,4,6-Tri-O-acetyl-2-bromo-2-deoxy-β-D-glucopyranosyl)-α-picolinium Perchlorate (24) (DMSO). (Acetyl signals at reduced amplitude).

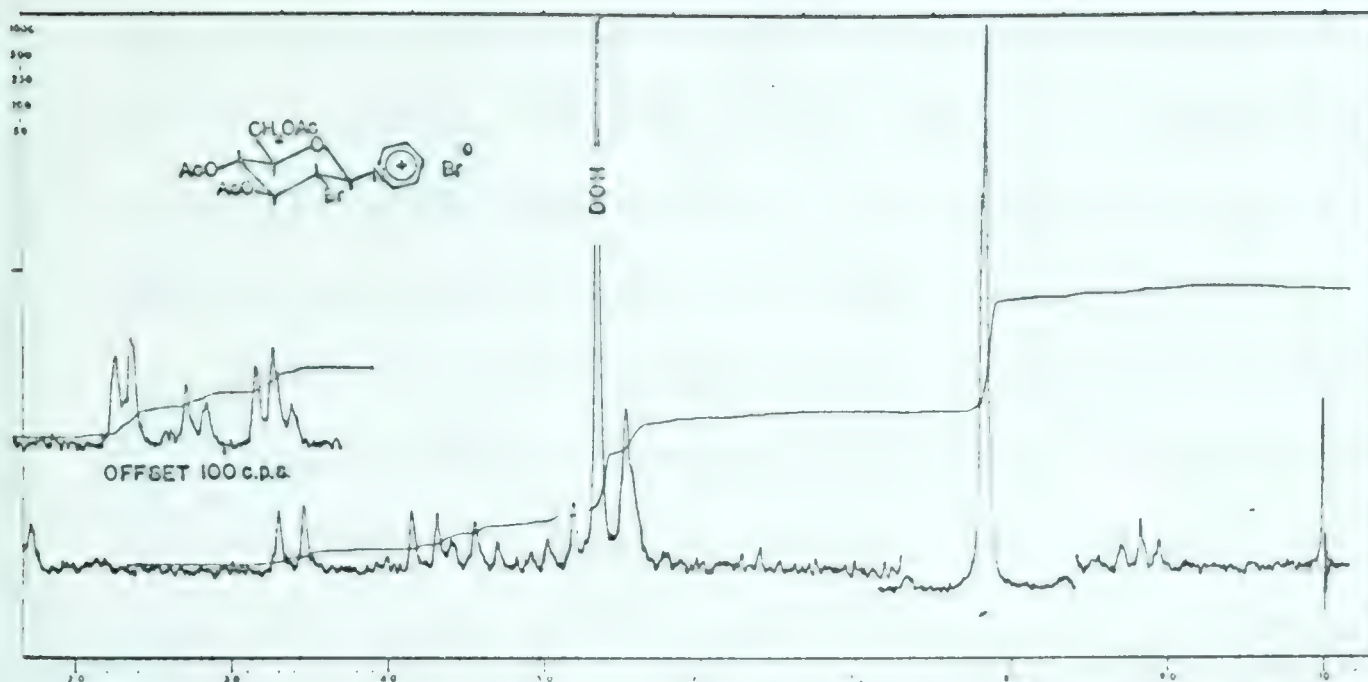


Fig. 19. $N-(3,4,6\text{-Tri-O-acetyl-2-bromo-2-deoxy-}\beta\text{-D-glucopyranosyl})\text{-pyridinium Bromide}$ (25) (Deuterium Oxide).



Fig. 20. The Non-crystallizable Product from the Reaction of Pyridine and Product of Bromine Addition to D-Glucal Triacetate (Deuterium Oxide) Experimental C.l.g.

signal of the anomeric proton of the α -manno-perchlorate isomer (Experimental C.1.f. and the above discussion) and the fact that tri-O-acetyl-2-bromo-2-deoxy- α -D-mannopyranosyl bromide was present to an extent of 30% in the starting material (45), in all probability the N-glycoside responsible for the spectrum shown in Fig. 20 has the β -manno-configuration.

N-(Tetra-O-acetyl- β -D-glucopyranosyl)-pyridinium bromide (26) was prepared following the directions of Fischer and Raske (69). The α -anomer of the chloride salt was obtained as a nearly pure syrup from reaction of tetra-O-acetyl- β -D-glucopyranosyl chloride with pyridine (Fig. 34). Consideration of the mechanism is left for later on. The configuration of the compound was concluded from an examination of the n.m.r. spectrum (Fig. 34) and comparing it with the spectrum (Fig. 25) for the crystalline N-(tetra-O-acetyl- α -D-glucopyranosyl)- γ -picolinium bromide (30) as well with the spectrum (Fig. 28a) of the nearly pure bromide salt (33). The reported value of the chemical shift for the anomeric proton of N-(tetra-O-acetyl- α -D-glucopyranosyl)-3-carboxamidopyridinium bromide at 2.94τ , spacing 3 c.p.s. (94), corresponds well with that of 3.12τ , spacing 3 c.p.s., obtained for 33 (Fig. 28a).

When α -acetobromoglucose was dissolved in γ -picoline, a reaction took place to give two crystalline compounds (29 and 30) which were readily identified from their n.m.r. spectra (Figs. 24 and 25). They were the expected products of the reaction, the α - and β - forms of N-(tetra-O-acetyl-D-glucopyranosyl)- γ -picolinium bromide. Compound 29 has an n.m.r. spectrum (Fig. 24 closely similar to that of the corresponding β -pyridinium bromide (26),

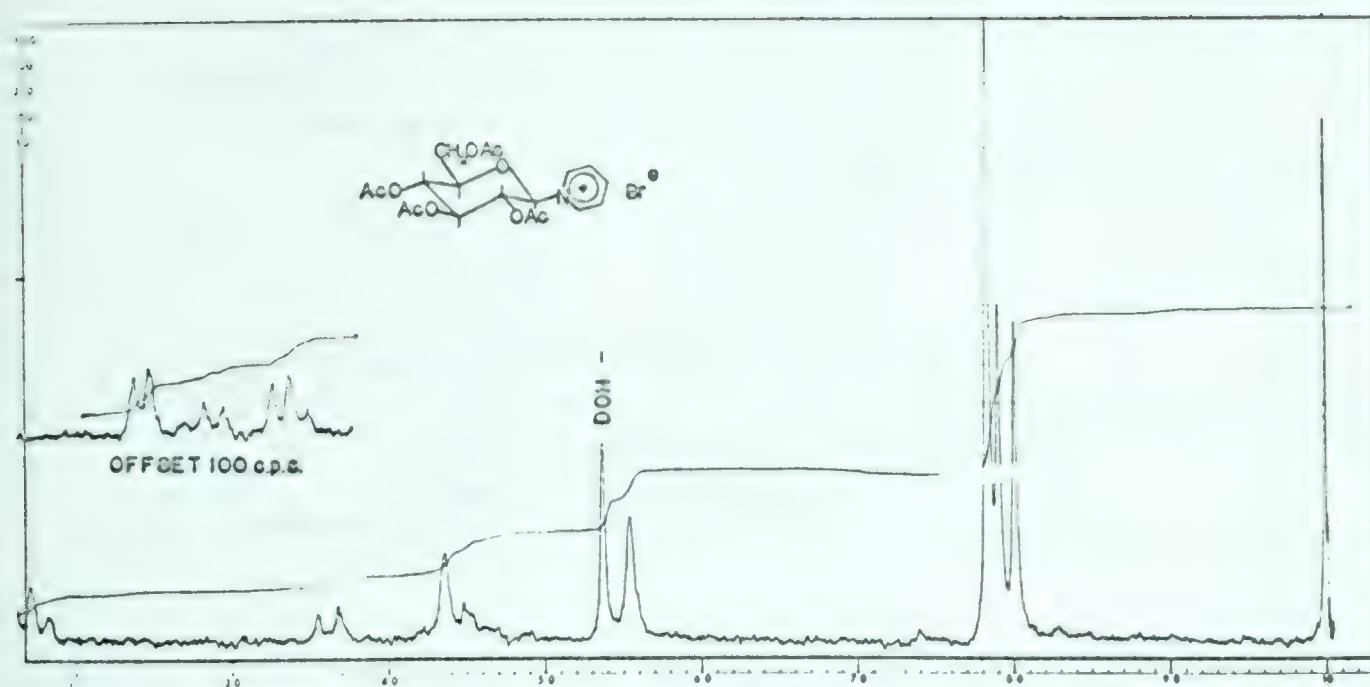


Fig. 21. N-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-pyridinium Bromide (26) (Deuterium Oxide).

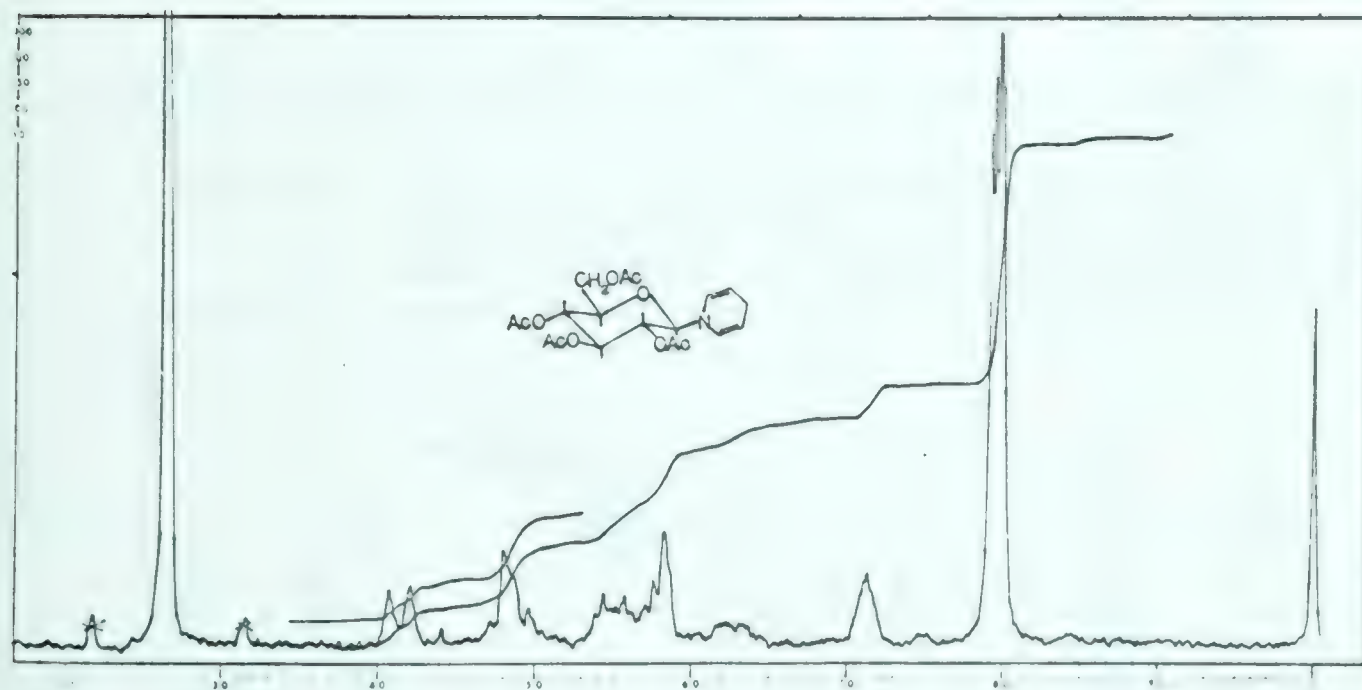


Fig. 22. N-Tetra-O-acetyl-β-D-glucopyranosyl-1,4-dihydropyridine (27) (Chloroform).

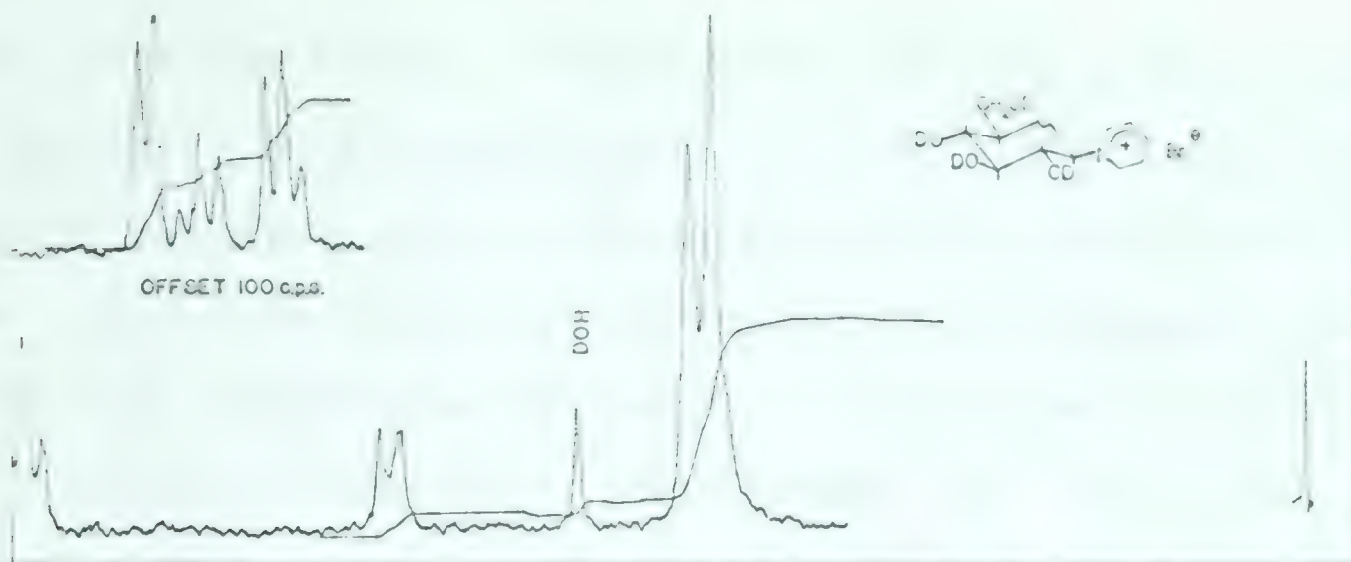


Fig. 23. N-β-D-Glucopyranosyl pyridinium Bromide (28) (Deuterium Oxide).

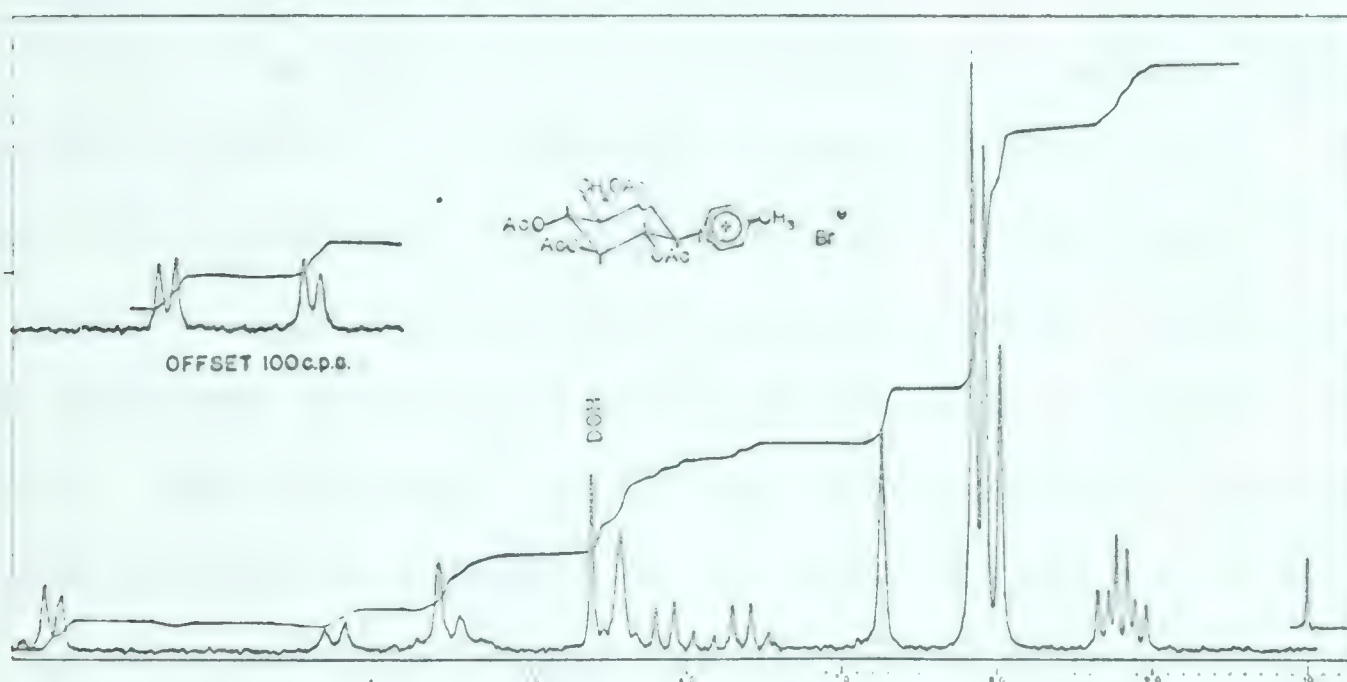


Fig. 24. N-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-γ-picolinium Bromide (29) with Solvated Ethanol, Ethyl Acetate and Water (Deuterium Oxide).

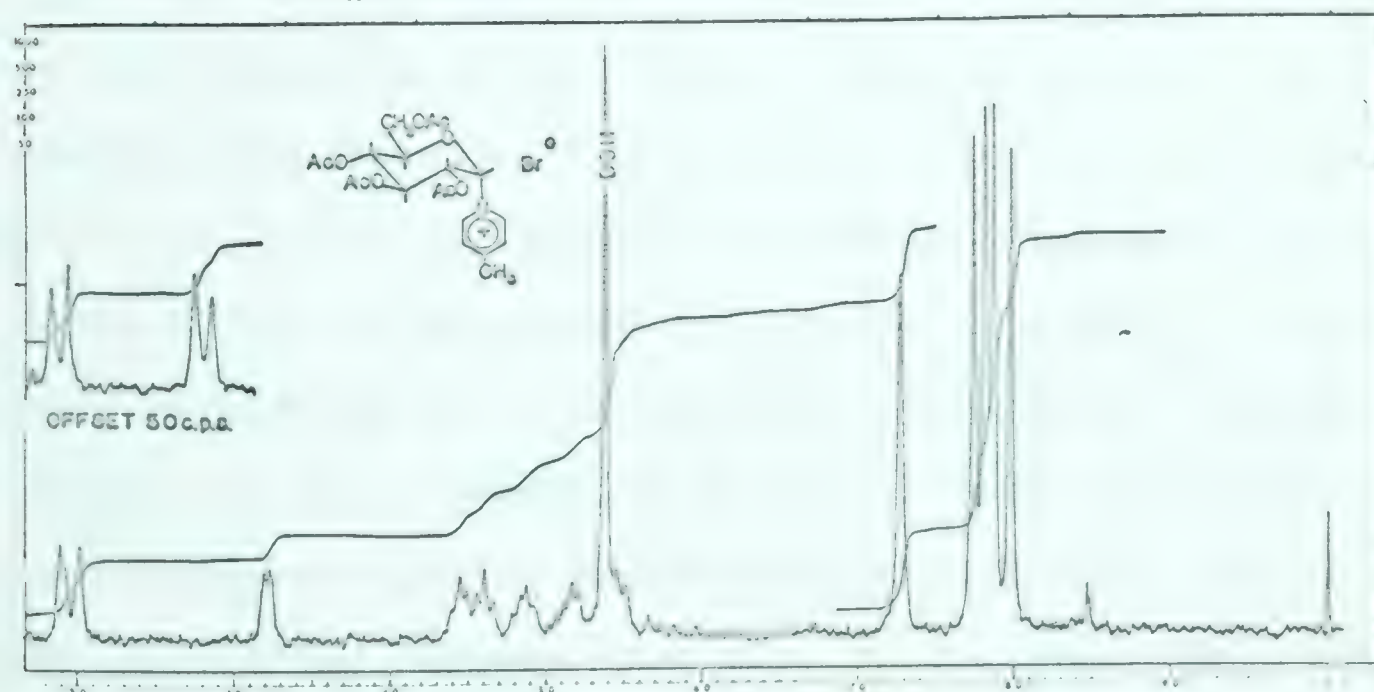


Fig. 25. N-(2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl)-γ-picolinium Bromide (30) (Deuterium Oxide).

except that the aromatic ring protons now form a simple A_2B_2 quartet and there is a methyl signal at 7.26τ . Also there are molecules of solvation corresponding to ethyl acetate, ethanol and water. The water could not be removed even in vacuo at 56° in the presence of phosphorous pentoxide, as determined by the analysis and the infrared spectrum. The α -anomer (30) has a n.m.r. spectrum (Fig. 25) that may be similarly compared with the corresponding pyridinium compound (33) (Fig. 28a).

Both the α - and β - γ -picolinium glucopyranosides (29 and 30) were deacetylated in 3% aqueous hydrogen bromide (71). Whilst the deacetylated β -anomer (31) was obtained crystalline, the deacetylated α -anomer (32) was obtained only as a syrup. Both structures were confirmed by an examination of the n.m.r. spectra (Figs. 26 and 27). The β -anomer (31) of N-(D-glucopyranosyl)- γ -picolinium bromide produced a doublet for its anomeric proton at 4.25τ , spacing 7 c.p.s., closely comparable with that of N-(β -D-glucopyranosyl)-pyridinium bromide (28) at 4.1τ , spacing 7 c.p.s. The α -anomer (32) has, as expected, an anomeric proton signal at 3.53τ , with a small spacing of 3.5 c.p.s. The remainder of the spectrum was exactly that expected for a γ -picolinium glucoside except for a small signal at 7.8τ , probably an impurity of some acetate.

Here it may be mentioned that the possibility of charge-transfer complexing was considered as a possible, if rather unlikely, reason for the instability of the C1 conformation of the pyridinium 2-deoxy-2-iodo- α -D-mannoside (19). Kosower (96) found that 1-alkyl pyridinium iodides give rise to charge-transfer bands from about $325\text{ m}\mu$ to $452\text{ m}\mu$ with a range for ϵ_{max} of 480 to 2700.

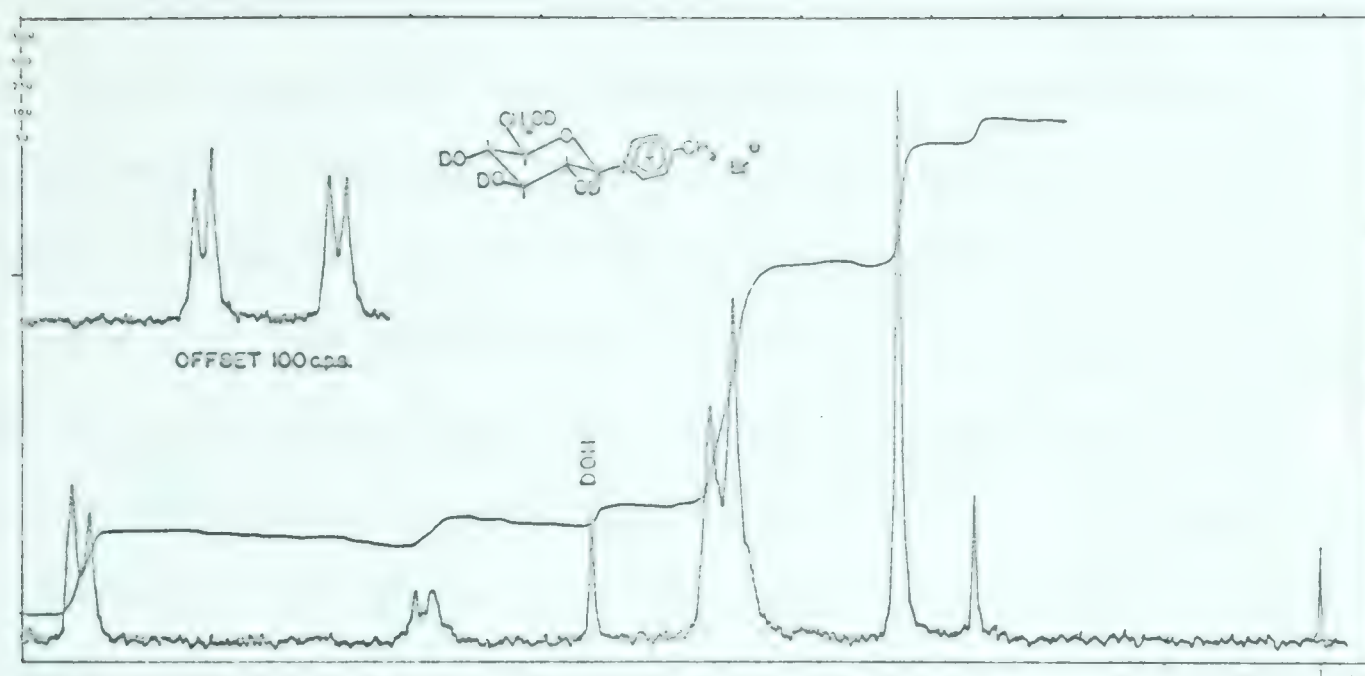


Fig. 26. Impure N-β-D-Glucopyranosyl-γ-picolinium Bromide (31) (Deuterium Oxide).

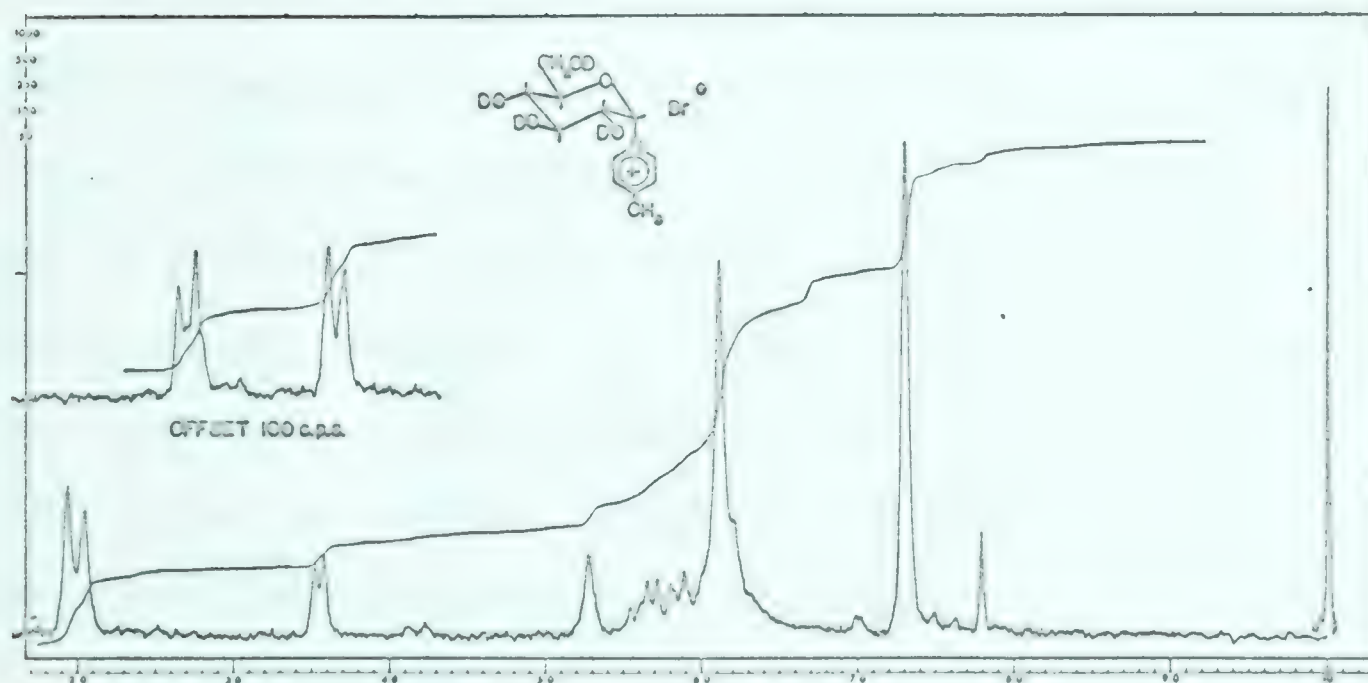


Fig. 27. Impure N-α-D-Glucopyranosyl-γ-picolinium Bromide (32) (Deuterium Oxide).

Since a linear relationship exists between the position of the charge-transfer light absorption and the ionization potential of the donor atom (96), any absorption in the 2-deoxy-2-iodo-nucleosides will be at considerably shorter wave-lengths due to the larger ionization potential of bound iodine over iodide ion. Unfortunately the pyridinium ion itself absorbs at around $260\text{ m}\mu$ (97) and ϵ_{max} 4000, so that any charge-transfer bands would be obscured by the much more intense pyridinium ion absorptions. Since the bromo-analog of 19 as discussed already probably exists in the same conformation as 19, and the possibility of charge-transfer complexing becomes very remote with the increasing ionization potential of the bound bromine atom, charge-transfer complexing probably has no connection with the unusual conformation of the 2-deoxy-2-halogeno- α -D-mannonucleosides.

The optical rotatory dispersion (o.r.d.) curves of 18 and 19 (Table I) were so interesting as to warrant the investigation of several pyridinium glycosides variously substituted. Since all the pyridinium glycosides studied absorb in the ultraviolet at about $260\text{ m}\mu$, and the o.r.d. curves can only be measured with any certainty down to $300\text{ m}\mu$, the maxima and minima of the Cotton effect curves are rarely observed. Thus the curves are classed as plain positive or plain negative (98).

The first indications that N-glycosides may not obey Hudson's rules of isorotation was the observation by Davoll and Lythgoe (99) that the more dextro-rotatory anomer of the acetylated 9-(2-deoxy-D-erythropentopyranosyl)-theophyllines provided on deacetylation the more levo-rotatory anomer of the free purine nucleosides. Fox

TABLE I

OPTICAL ROTATORY DISPERSION CURVES OF
QUATERNARY N-GLYCOSIDES

Structure	λ m μ \rightarrow	Conc.	$[\alpha]_D$										
			300	350	400	450	500	550	600	650	700		
N-(3,4,6-Tri-O-acetyl-2-deoxy-2-iodo- β -D-glucopyranosyl)-pyridinium Perchlorate (18)	0.05 H ₂ O		1270	604	400	298	247	211	189	167	138		
	1.1 MeOH		1050*	518	306	216	158	124	100	81	69		
N-(3,4,6-Tri-O-acetyl-2-deoxy-2-iodo- α -D-mannopyranosyl)-pyridinium Perchlorate (19)	0.09 H ₂ O		-380	-92	-4.3	0	0	0	0	0	0		
	0.1 H ₂ O		1610	595	301	239	214	194	157	144	144		
N-(2-Deoxy-2-iodo- β -D-glucopyranosyl)-pyridinium Perchlorate (20)	0.1 H ₂ O		690	377	253	140	68	45	20	0	0		
	0.5 MeOH		635	323	212	153	113	89	72	59	50		
N-(3,4,6-Tri-O-acetyl-2-bromo-2-deoxy- β -D-glucopyranosyl)-pyridinium Bromide (25)	1.2 MeOH		-	332	217	154	115	93	77	64	55		
	0.16 MeOH		1255	541	346	250	198	163	143	126	119		
N-(3,4,6-Tri-O-acetyl-2-bromo-2-deoxy- β -D-glucopyranosyl)- α -picolinium Perchlorate (23)													
N-(3,4,6-Tri-O-acetyl-2-bromo-2-deoxy- β -D-glucopyranosyl)- α -picolinium Perchlorate (24)	0.36 MeOH		758	348	214	147	108	83	66	51	45		

* λ m μ 307

TABLE I (Continued)

Structure	λ m μ \rightarrow	Conc.	$[\alpha]_D$									
			300	350	400	450	500	550	600	650	700	
See Figure 20, Experimental C.1.g.	3.1 MeOH		-	-	-75	-54	-40	-31	-25	-21	-17	
N-(2,3,4,6-Tetra-O-acetyl- β -D-glucopyranosyl)-pyridinium Bromide (26)	1.5 MeOH		-	-70	-38	-23	-16	-12	-9	-7	-5	
N- β -D-Glucopyranosyl pyridinium Bromide (28)	1.2 H ₂ O		167	126	91	70	58	50	42	35	33	
N-(2,3,4,6-Tetra-O-acetyl- β -D-glucopyranosyl)- γ -picolinium Bromide (29)	1.0 H ₂ O		-128	-61	-35	-22	-17	-13	-9	-7	-6	
Impure N- β -D-Glucopyranosyl- γ -picolinium Bromide (31)	1.2 MeOH		-	127	92	70	55	45	37	31	26	
Impure N- α -D-Glucopyranosyl- γ -picolinium Bromide (32)	1.6 H ₂ O		267	175	125	94	73	59	50	41	36	
Impure N-(2,3,4,6-Tetra-O-acetyl- α -D-glucopyranosyl)-pyridinium Bromide (33) Fig. 28a	1.0 MeOH		49*	57	51	41	33	29	25	21	20	
N-(2,3,4,6-Tetra-O-acetyl- α -D-glucopyranosyl)- γ -picolinium Bromide (30)	1.0 H ₂ O		138	121	90	66	51	40	33	27	26	

* λ m μ 325

and coworkers (100) reported several pairs of anomeric 1-(2'-deoxy-D-ribofuranosyl)-pyrimidines which were exceptions to Hudson's rules of isorotation. Lemieux and Hoffer (101) have confirmed the assignment of the anomeric configuration of some 1-(2'-deoxy-D-ribofuranosyl)-pyrimidines by n.m.r., and they published the o.r.d. curves for the pairs of anomeric 1-(2'-deoxy-D-ribofuranosyl)-5-methyluracil and the corresponding 5-fluorouracil. These pairs of anomers not only disobey Hudson's rules of isorotation in water, but the α -anomers show plain negative o.r.d. curves whilst the β -anomers show plain positive curves. Recently (102) it was shown that Hudson's rules cannot be employed to assign anomeric configuration to pyrimidine nucleosides in general. Lemieux and Lown (94) prepared both anomers of N-(tetra-O-acetyl-D-glucopyranosyl)-3-carboxamidopyridinium bromide and their deacetylated products. The o.r.d. curves for these 4 compounds were exactly analogous to the results we obtained with the pyridinium and γ -picolinium analogs. The most noteworthy feature was that the deacetylation of the β -anomers (26,29) which have negative curves, led to products (28,31) with positive curves. By way of contrast, the α -anomers (33,30) have positive curves, and the deacetylated product of 30 (32) also has a positive curve. The prediction of the sign of the curve becomes still more complex when it was observed that N-(2,3,4,6-tetra-O-acetyl- β -D-mannopyranosyl)-pyridinium bromide (103) whilst having a negative rotation at the sodium D-line has a positive o.r.d. curve and has a positive rotation near 300 m μ . All the N-(2-deoxy-2-halogeno-D-glucopyranosyl)-pyridinium salts and their derivatives in the β -series have positive o.r.d. curves, and

compound 19 with the α -manno-configuration has a negative curve. Unfortunately we have not succeeded in forming true crystalline anomers in the pyridinium 2-deoxy-2-halogeno-D-glycoside series. An attempt to do so was made by reacting D-glucal triacetate with bromine which is known to give 3,4,6-tri-O-acetyl-2-bromo-2-deoxy- α -D-manno- and α -D-gluco-pyranosyl bromide (45). Lemieux and Fraser-Reid (45) observed Walden inversion at the anomeric center when the products of bromine addition to D-glucal triacetate were methoxylated. Thus the expected products on reaction of the mixture of the latter compounds with pyridine are N-(3,4,6-tri-O-acetyl-2-bromo-2-deoxy- β -D-glucopyranosyl)-pyridinium bromide (25) and the β -D-manno-isomer. The former 25 was actually isolated and the latter was deduced to be present in the crude syrup obtained from the mother liquors, as already discussed. The o.r.d. curve of the syrup giving the n.m.r. spectrum shown in Fig. 20 is negative. Therefore it appears that N-(3,4,6-tri-O-acetyl-2-bromo-2-deoxy- β -D-mannopyranosyl)-pyridinium bromide's o.r.d. curve unexpectedly has the opposite sign to the β -gluco-analog (25) and the same sign as the 2-deoxy-2-iodo- α -D-manno-compound (19) and hence probably the bromo-analog of 19. It is obvious therefore that before a comprehensive theory relating the sign of the o.r.d. curves to the structure, stereochemistry and configuration of nucleosides can be made, many more model compounds must be studied. The applications of o.r.d. to steroids and the elucidation of the octant rule (104) encourage one to enlarge the use of this new tool to include carbohydrates (105) and in particular nucleosides. Because of the possible application of such a theory to the nucleic

acid field, it would be of great interest to have some working hypothesis. A reasonable postulate, also consistent with Brewster's model (83) of a screw pattern of polarizability, is that the sign of the Cotton curve, which will be intimately associated with the ultraviolet absorption of the pyridinium ring, must be determined by the relative orientations of the pyridinium and glycopyranose rings. It is also evident that the 2-substituent plays a very important part in the sign of the o.r.d. curve and hence probably on the orientation of the pyridinium ring.

The mechanism of the formation of 2-deoxy-2-halogen-N-glucosides will be expected to be basically the same as that proposed by Lemieux and Levine (44) for the formation of 2-deoxy-2-halogeno-O-glycosides. However, whereas in the formation of O-glycosides the α -manno-configuration predominated, for quaternary N-glycosides the β -gluco-configuration predominated. In each case it is the thermodynamically more stable configuration, on the basis of the anomeric effect (14,15), that is formed in greater yield. This confirms the initial reversible attack by the positive halogen on the π -bond. Otherwise one should obtain roughly the same ratio of the α -manno- and β -gluco-configurations whatever the nucleophile, and only solvents effects would alter the ratio. But these reactions were carried out in chloroform, and the complete reversal of the dominant configuration suggests that there is a rapid reversible attack by the halonium ion at the double bond. This is followed by the rate determining step, which involves attack by the nucleophile to give a transition state which reflects the anomeric effect. Hence the more stable configuration

is obtained. It may be objected that since the 2-deoxy-2-iodo- α -D-manno-compound (19) rearranged in pyridine to the β -gluco-configuration of 18, that the high yield of 18 was due to such isomerization in the reaction mixture. However, the isomerization in pyridine was slow whereas the reaction in chloroform was rapid. Also pyridine with a dielectric constant approximately 3 times greater than that of chloroform should more readily facilitate charge separation to enable the rearrangement to take place, apart from stabilizing the halonium ion formed. Thus it may be safely concluded that the initial ratio of 18 and 19 corresponds closely to that of the isolated products.

C. KINETIC AND MECHANISTIC STUDIES ON THE REACTION OF PYRIDINE WITH 2,3,4,6-TETRA-O-ACETYL- α -D-GLUCOPYRANOSYL BROMIDE

In view of the rather interesting o.r.d. properties of the pyridinium 2-deoxy-2-halogeno-glycosides reported in the previous Section, it was decided to prepare N-(2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl)-pyridinium bromide (26). Fischer and Raske (69) prepared this compound through the reaction of α -acetobromoglucose with pyridine in the presence of phenol. On repeating the preparation compound 26 was obtained, 47% yield, and its anomeric configuration confirmed by the n.m.r. spectrum shown in Fig. 21. The doublet at 3.66 τ , spacing 8 c.p.s. is in keeping with the β -D-gluco-configuration. Since the role of the phenol in the reaction mixture was not evident, it was decided to examine the course of the reaction in its absence. When 35.33 g of α -acetobromoglucose reacted with 50 ml of pyridine to constant rotation, a syrupy,

water-soluble product was obtained which gave the n.m.r. spectrum shown in Fig. 28. Along with the signal for the anomeric proton of the above described compound, 26, a signal is obtained at 3.12τ , spacing 3 c.p.s., which could be assumed to arise from the presence in the mixture of the α -anomer of 26. The relative intensities of the signals indicated that the two compounds were present in the ratio 3:1 in favour of the presumed α -anomer. β -Acetochloroglucose (tetra-O-acetyl- β -D-glucopyranosyl chloride) was reacted with pyridine at room temperature. To the syrupy product obtained, water was added, and the mixture was extracted with chloroform. The chloroform extract gave a syrup, the n.m.r. spectrum of which showed it to be mainly α -acetochloroglucose. Evaporation of the aqueous phase gave a syrup which was assigned the structure N-(tetra-O-acetyl- α -D-glucopyranosyl)-pyridinium chloride as already discussed in Section B. It was therefore established that the reaction of α -acetobromoglucose with pyridine under the above conditions indeed gave in part (about 70%) the α -anomer of 26. When as much as possible of the β -anomer was removed by crystallization, the n.m.r. spectrum (Fig. 28a) of a fairly pure sample of the α -anomer was obtained.

The change in optical rotation during the reaction of α -acetobromoglucose with pyridine was followed polarimetrically (Diag. 2, Curve (i)) and it corresponded closely to a first-order process with a rate constant, k , of $1.2 \times 10^{-3} \text{ min}^{-1}$ (common logarithms) when the initial concentration of α -acetobromoglucose was low, 1.9% (w./v.). Virtually only the β -anomer (26) was formed, as seen from the n.m.r. spectrum shown in Fig. 30. Since it was found that the

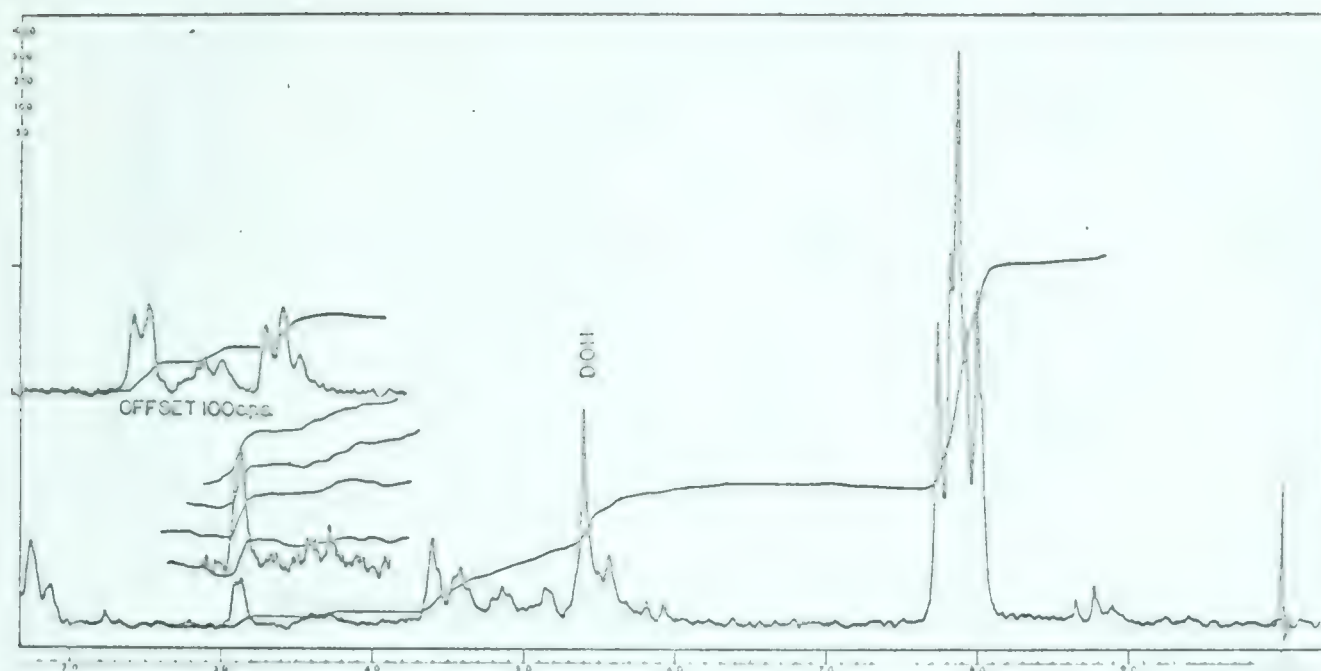


Fig. 28. The Product of the Reaction of Tetra-O-acetyl- α -D-glucopyranosyl Bromide with Pyridine, Experimental C.3.a. (Deuterium Oxide).

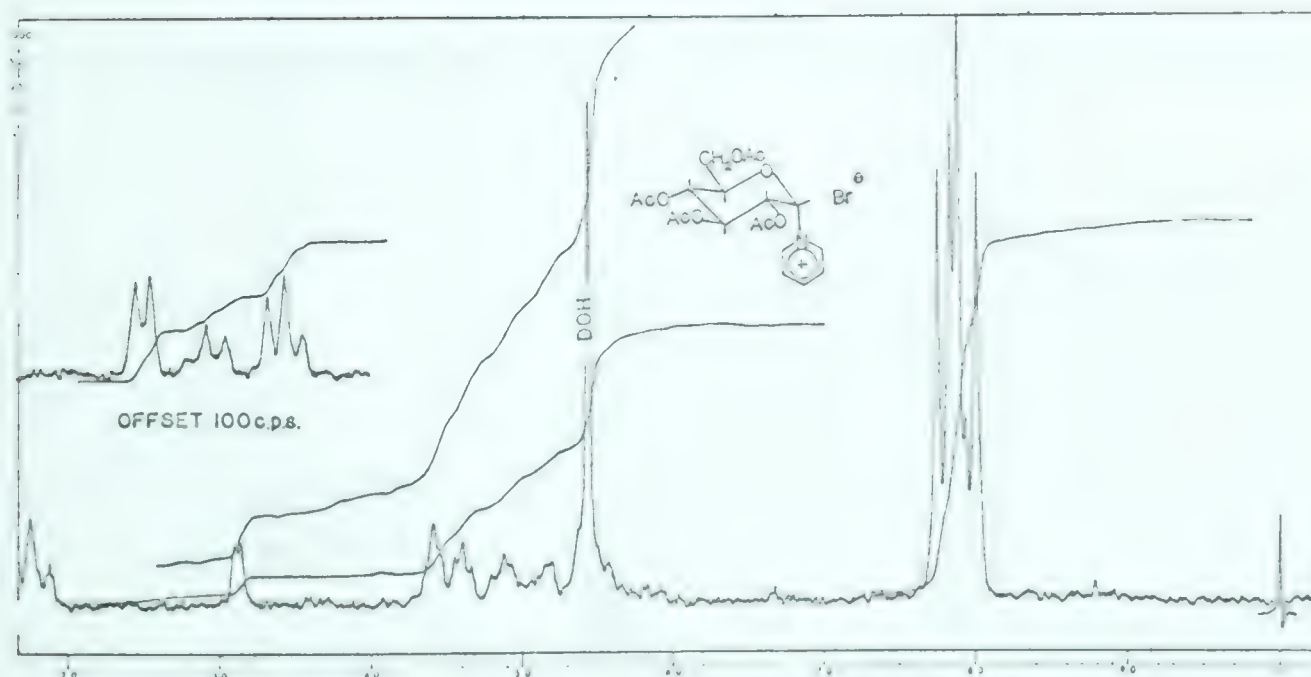


Fig. 28a. Impure N-(2,3,4,6-Tetra-O-acetyl- α -D-glucopyranosyl)-pyridinium Bromide (33) obtained from the Product shown in Fig. 28 after Removal of the β -Anomer (26) by Crystallization (Deuterium Oxide).

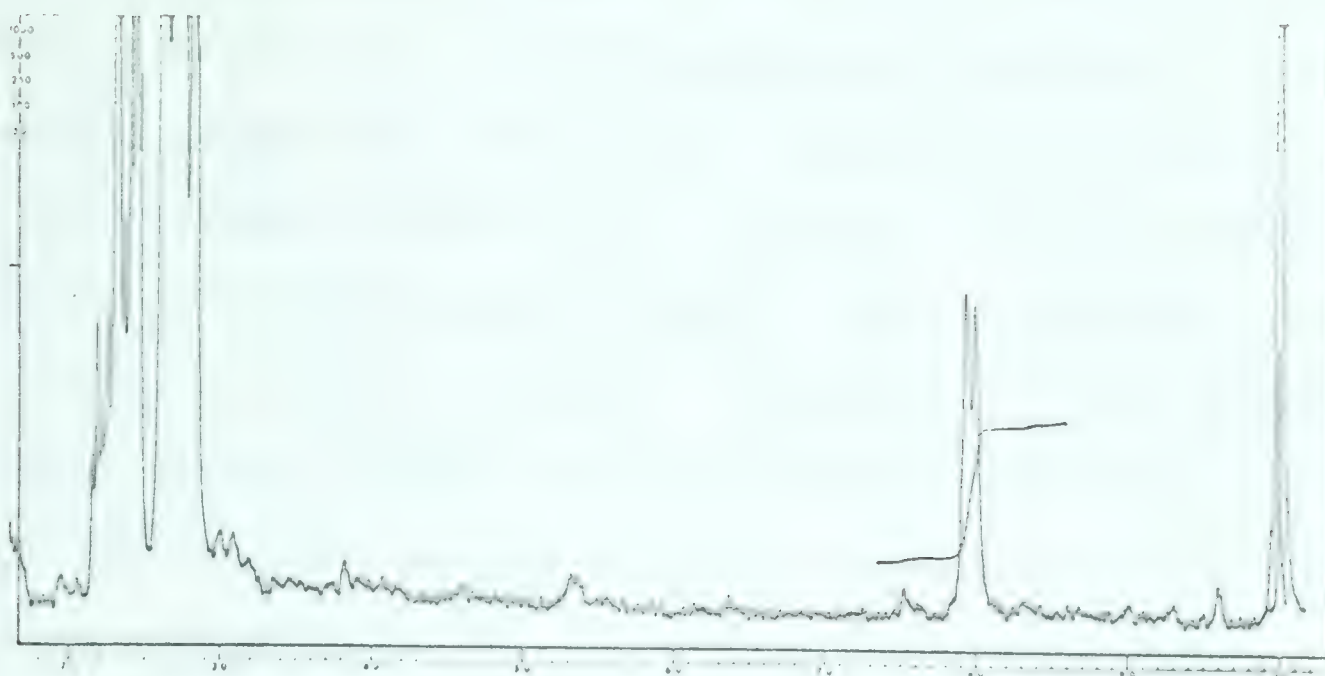


Fig. 29. Mainly N-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-pyridinium Bromide (26), Experimental C.3.a.(i). (Pyridine).

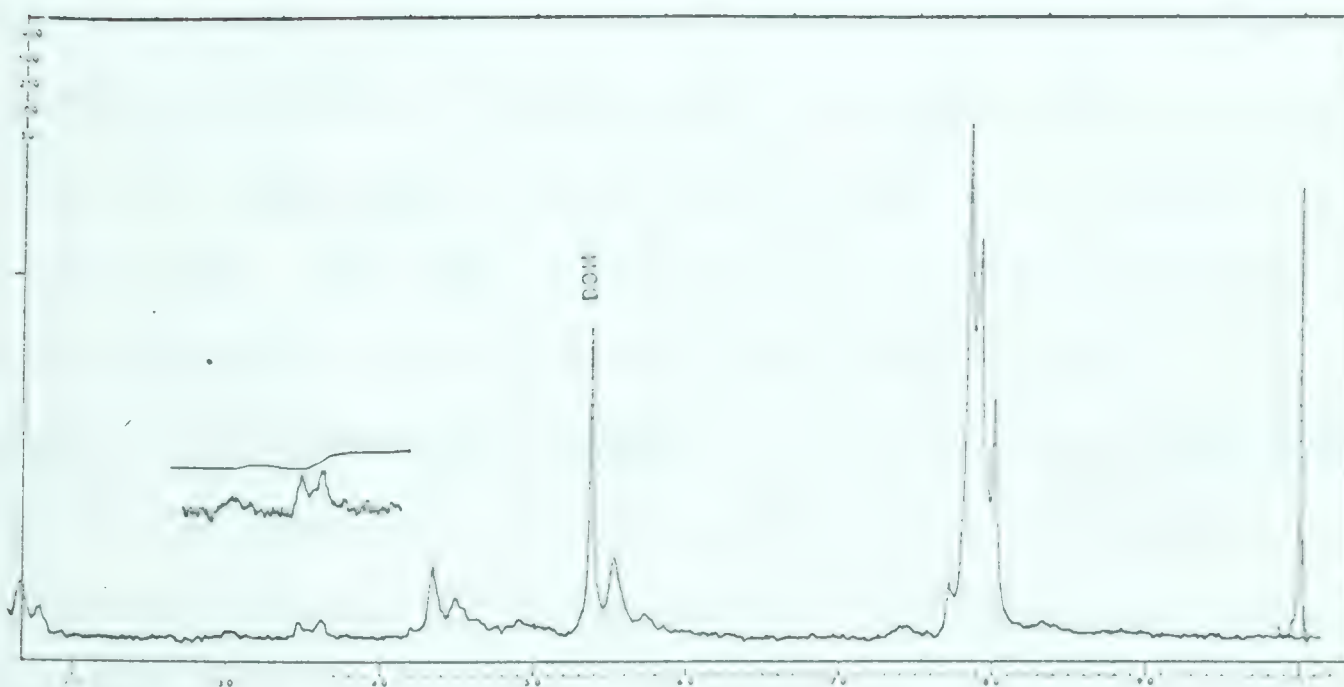


Fig. 30. As for Fig. 29 (Deuterium Oxide).

n.m.r. spectrum of the α -anomer (33) in pyridine contained an acetyl signal considerably to lower field, 7.47τ , than the other acetyl groups, a check was made by examining a spectrum in pyridine as well, Fig. 29. There is a small trace of the acetyl signal attributable to the α -anomer at about 7.5τ . However, when the initial concentration of α -acetobromoglucose was 34.4%, an induction period was noted (Diag. 2, Curve (iii)) and, therefore, it was apparent that the product of the initial reaction became involved in a faster process. That this was not due to a change in the polarity of the medium or due to salt effects, was shown in a later experiment. The relative amounts of the α - and β -anomeric forms was now about 56:44, (Fig. 32) or, when calculated from the low field acetyl signal in Fig. 31, 53:47.

The induction period was also present when the initial concentration of α -acetobromoglucose was about 16%, and the anomers were formed in about equal amounts. The same course of reaction was obtained when half of the pyridine was replaced by acetonitrile, although the more polar solvent gave rise to a somewhat increased rate of reaction. When the reaction of α -acetobromoglucose (16% initial concentration) was carried out in pyridine containing one mole of tetra-*n*-butylammonium bromide per mole of α -acetobromoglucose, the rate of the reaction was much greater and the induction period was not present (Diag. 2, Curve (iv)). Virtually only the α -pyridinium glucoside (33) was formed, (compare the n.m.r. spectrum of the product, Fig. 33, with those in Figs. 28a and 34). When tetra-*n*-butylammonium perchlorate was used instead of the bromide, the induction period reappeared and the product comprised a 2:3 mixture of the β - and α -forms respectively.

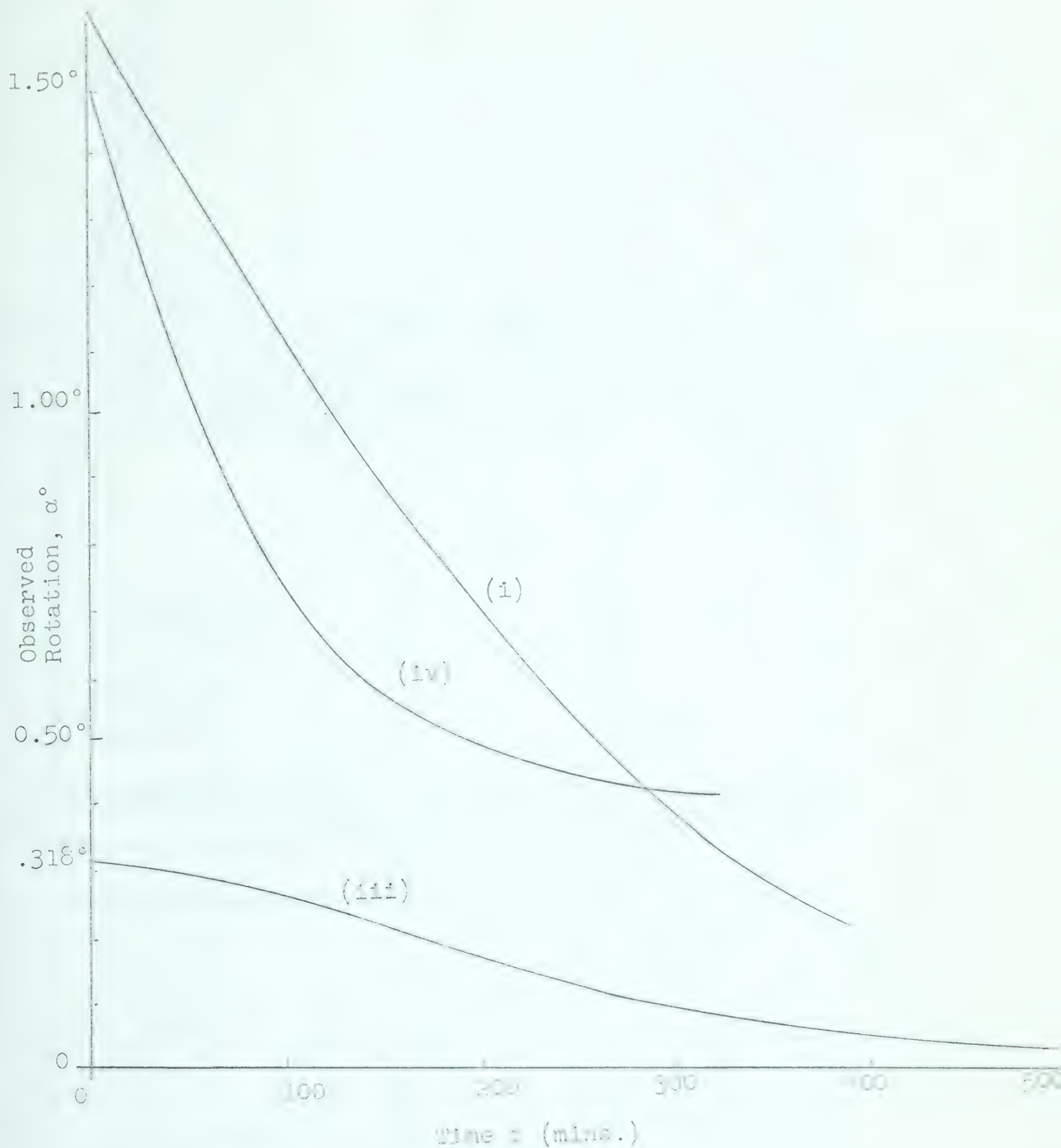


Diagram 2. The polarimetric rates of reaction of 2,3,4,6-tetra-*o*-acetyl- α -D-glucopyranosyl bromide with pyridine, (Experimental C.3.a, p. 37); (i) 1.9% (w./v.) of the bromide, $t \times 0.5$, α displaced downwards by 0.4° ; (iii) 34.4% (w./v.) of the bromide, $\alpha \times 0.01$; (iv) 16% (w./v.) of the bromide and equimolar tetra-*n*-butylammonium bromide, $\alpha \times 0.1$.

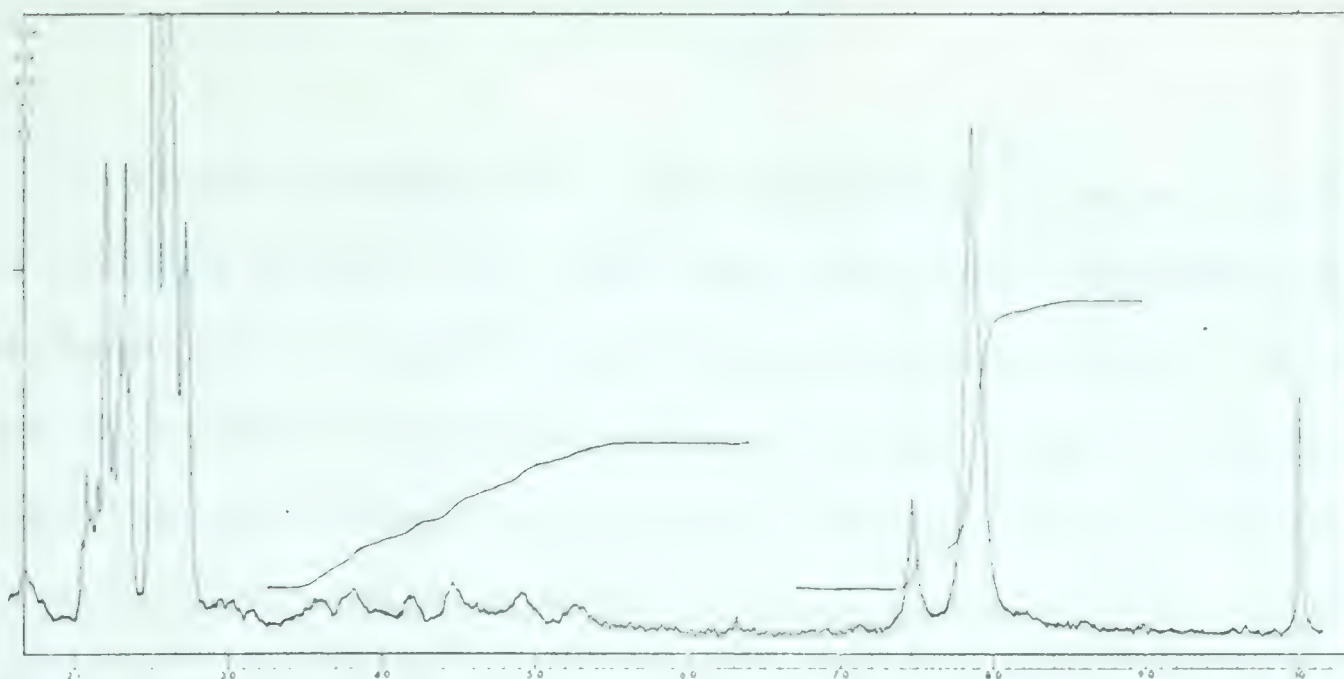


Fig. 31. Mainly N-(2,3,4,6-Tetra-O-acetyl- α -D-glucopyranosyl)-pyridinium Bromide (33), Experimental C.3.a.(iii). (Pyridine).

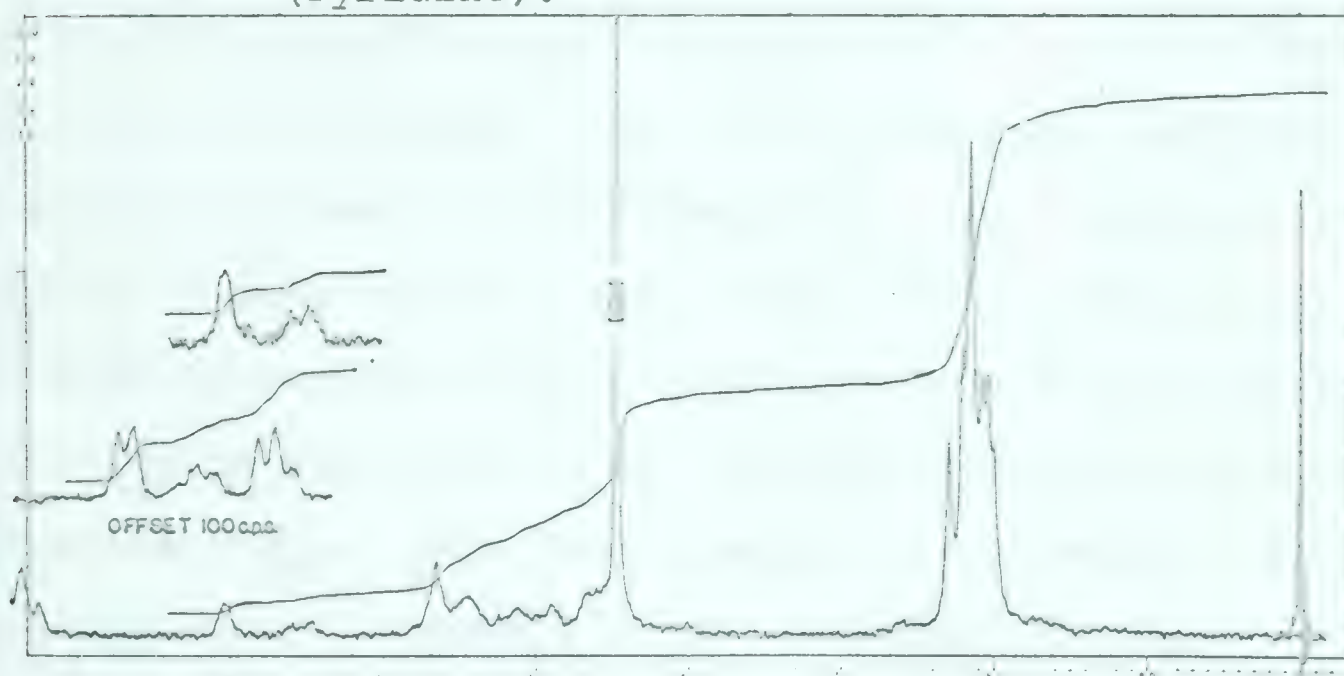


Fig. 32. As for Fig. 31 (Deuterium Oxide).

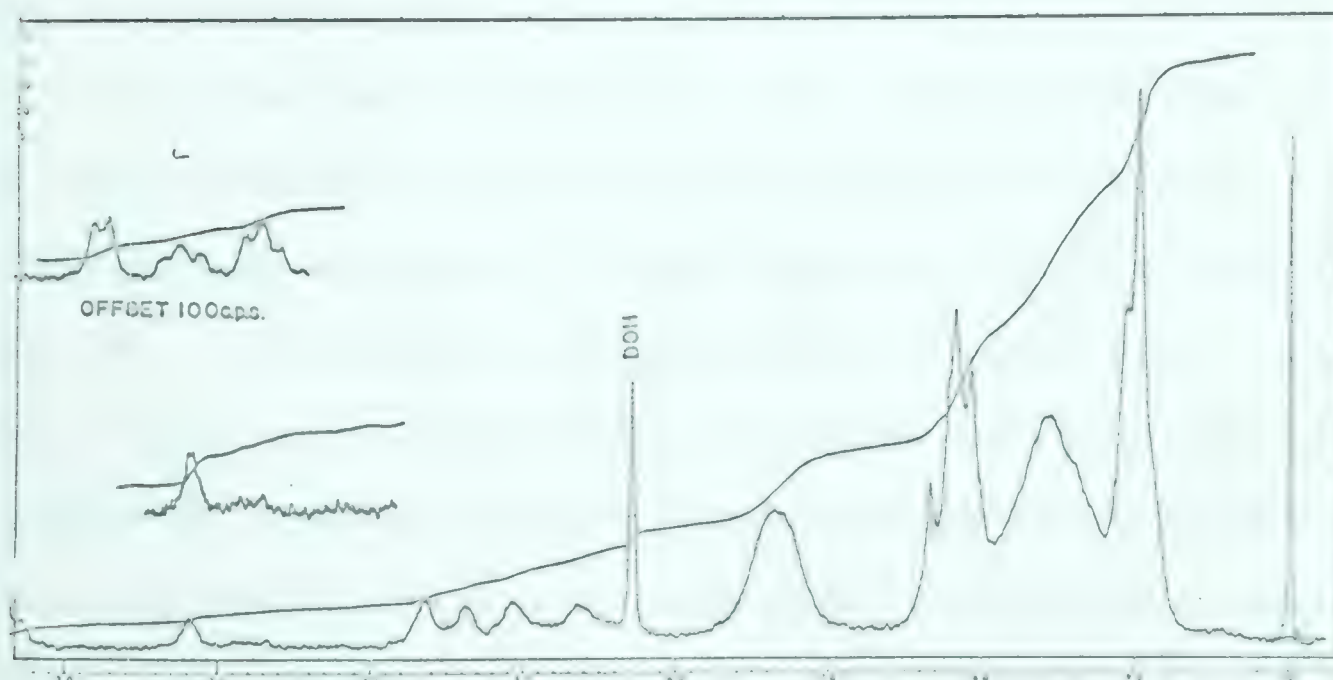


Fig. 33. Mainly N-(2,3,4,6-Tetra-O-acetyl- α -D-glucopyranosyl)-pyridinium Bromide (33) and Tetra-n-butyl Ammonium Bromide, Experimental C.3.a. (Deuterium Oxide).

The most reasonable interpretation of these results was that an initial reaction in which the α -acetobromoglucose underwent nucleophilic attack by pyridine with inversion of the anomeric center produced the β -pyridinium bromide (26). The bromide ion thus liberated then participated in the faster process by making a nucleophilic attack on α -acetobromoglucose to form its anomer, tetra-O-acetyl- β -D-glucopyranosyl bromide. It is conceivable that the α -pyridinium glucoside (33) was formed by direct displacement of the equatorially orientated bromine by pyridine with inversion of the anomeric center. If so this reaction would have to be very rapid as compared to the formation of the β -pyridinium glucoside (26) from α -acetobromoglucose since the results require the formation of tetra-O-acetyl- β -D-glucopyranosyl bromide to be rate controlling in the sequence of reactions leading to the α -pyridinium glucoside (33). Also the concentration of tetra-O-acetyl- β -D-glucopyranosyl bromide must be very small throughout the course of the reaction since, through the anomeric effect (14,15) it is the thermodynamically less stable anomer.

It seemed more likely that the rapid formation of 33 by way of the β -bromide would involve participation of the 2-acetoxy-group in the reaction of the β -bromide, to lead to a 1,2-acetoxonium ion. In fact the β -bromide has recently been isolated (106) and its reaction properties correspond to those previously established for tetra-O-acetyl- β -D-glucopyranosyl chloride (67). Since the reaction of the latter compound in pyridine containing an alcohol leads to the formation of α -D-glucopyranose 1,2-(alkyl orthoacetate) triacetate (47,67), those observations related to the

formation of the α -pyridinium glucoside (33) led to the prediction that the addition of α -acetobromoglucose to pyridine containing methanol would result in the formation of the 1,2-(methyl orthoacetate) (50). In fact the reaction of α -acetobromoglucose in pyridine containing 3 moles of methanol per mole of α -acetobromoglucose, under conditions which in the absence of methanol provided the α - and β -pyridinium glucosides in the ratio 3:2, gave as the product a mixture of the methyl orthoacetate and the β -pyridinium glucoside, (Figs. 35 and 36 respectively). That is the presence of the methanol blocked the route to the formation of the α -pyridinium glucoside (33), precisely the result expected should the latter compound arise from the 1,2-acetoxonium ion intermediate. The n.m.r. spectrum of the 1,2-orthoacetate, (Fig. 35) showed the presence of the two possible diastereoisomers arising from a change in the configuration of the new asymmetric center in the dioxalane ring (56). The isomer which produced signals for the methoxy and orthoacetyl groups at 6.70τ and 8.28τ , respectively, is believed on the basis of the n.m.r. spectrum (56) and through steric approach control (47) to have the structure in which the alkoxy group is exo (56) (Discussion D).

In order to confirm these notions the reaction of tetra-O-acetyl- β -D-glucopyranosyl chloride with pyridine was examined. As already seen with regard to the characterization of 33 and as expected, the only water soluble product isolated was the α -pyridinium glycoside, as proved by the n.m.r. spectrum shown in Fig. 34. It was therefore possible to conclude that the α -anomer 33 is formed by way of β -acetobromoglucose. Furthermore it was evi-

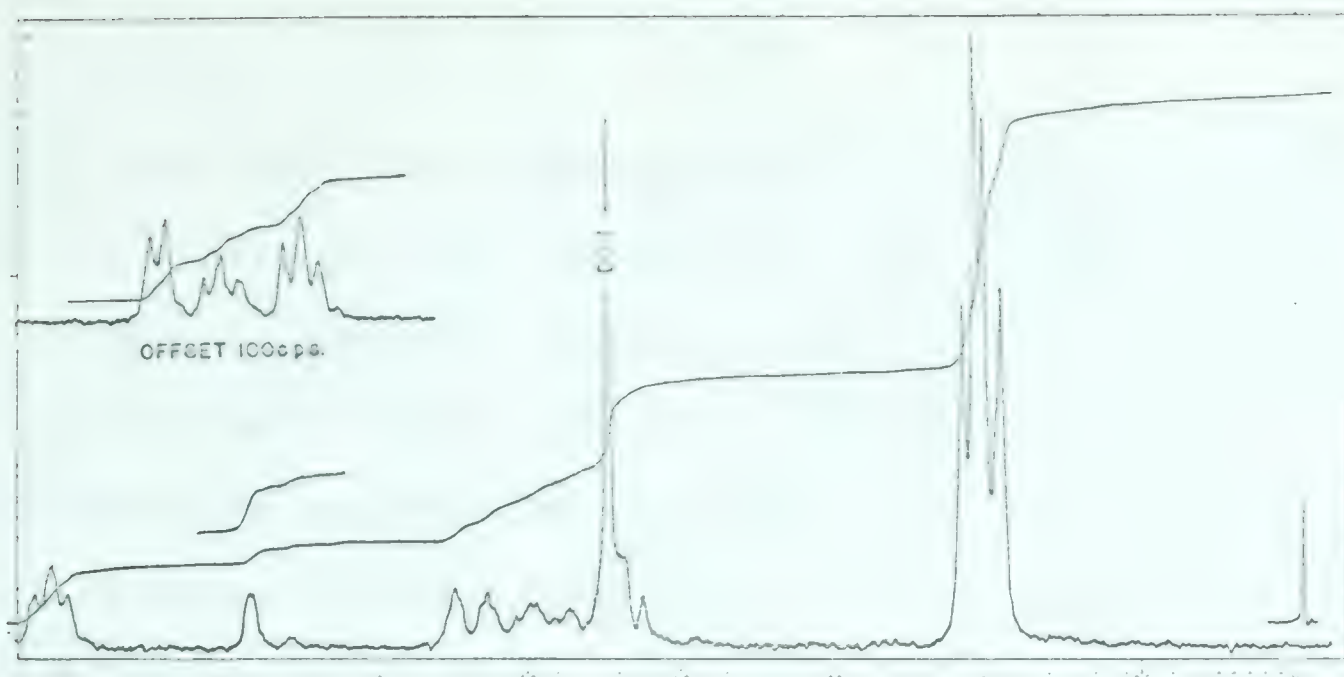


Fig. 34. Impure N-(2,3,4,6-Tetra-O-acetyl- α -D-glucopyranosyl)-pyridinium Chloride, Experimental C.3.a.(viii). (Deuterium Oxide).

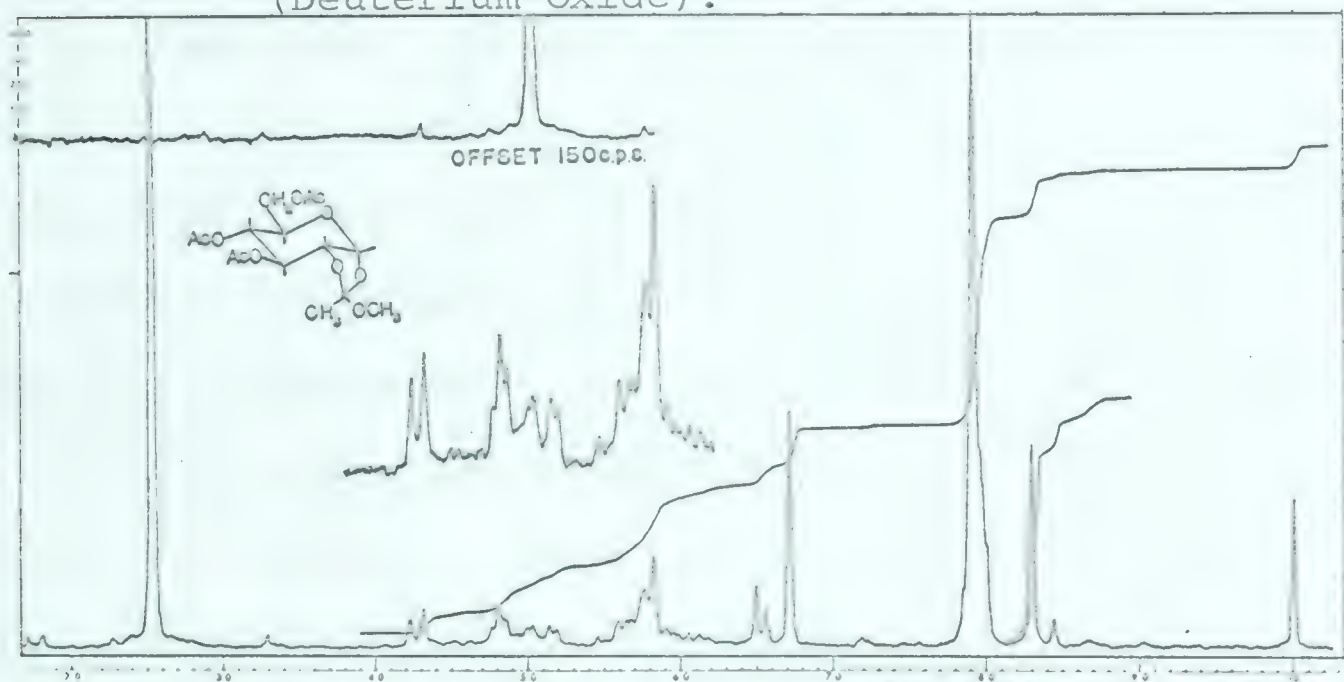


Fig. 35. Crude α -D-Glucopyranose 1,2-(Methyl Orthoacetate)-3,4,6-triacetate, Experimental C.3.a.(ix). (Chloroform).

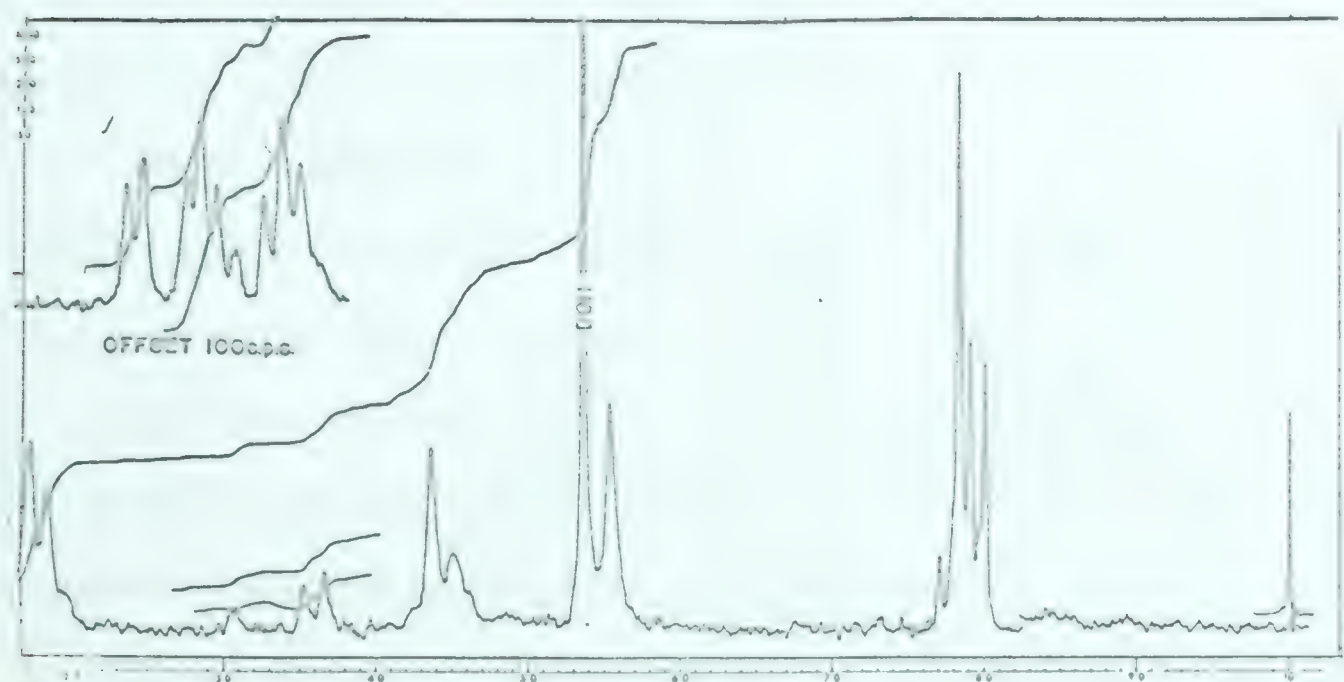


Fig. 36. Mainly N-(2,3,4,6-Tetra-O-acetyl- β -D-glucopyranosyl)-pyridinium Bromide (26), Experimental C.3.a.(ix). (Deuterium Oxide).

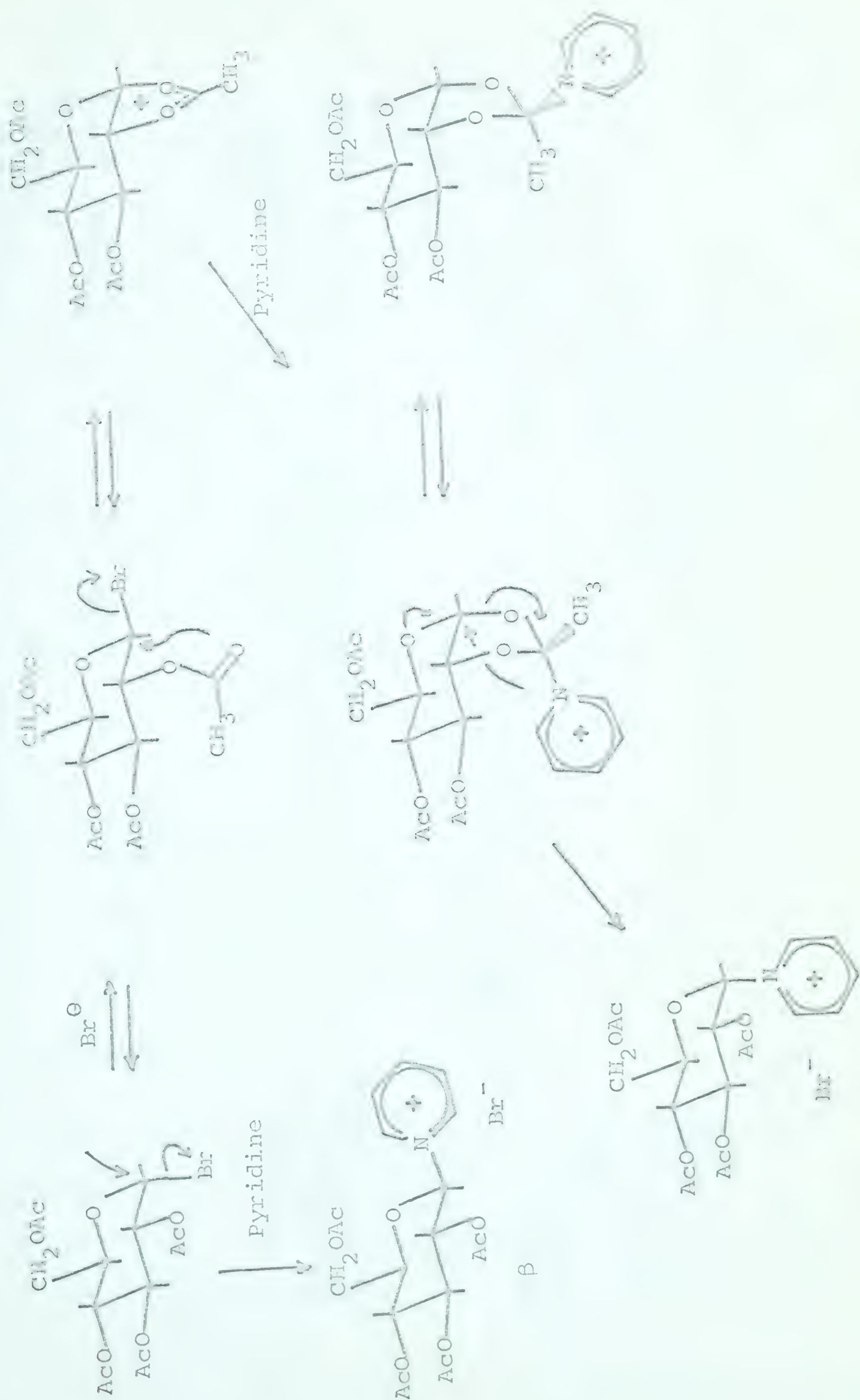
dent that the β -acetobromoglucose dissociated to 1,2-acetoxonium ion at a rate at least as great as the formation of 33. Therefore unless β -acetobromoglucose reacts with pyridine to form the α -pyridinium compound (33) at a much greater rate than α -acetobromoglucose reacts with pyridine to form the β -anomer (26) and unless the 1,2-acetoxonium ion tends to react with bromide ion to give β -acetobromoglucose at a rate much greater than its reaction with pyridine to form the β -pyridinium compound (26), then it must be concluded that 33 arises from the 1,2-acetoxonium ion. It is therefore most probable that the driving force for the ready formation of 33 from β -acetobromoglucose is derived from the anchimeric assistance provided by the participation of the 2-acetoxy group and that, consequently, the last stage of the reaction involved an intramolecular rearrangement of a transient 1,2-orthoacetyl pyridinium bromide. These reactions are summarized in Scheme II. That the mixtures of β - and α -pyridinium glucosides (26 and 33) were not formed by anomerization was confirmed by the stability of 26 in pyridine. In Scheme III is summarized the data pertaining to the elucidation of Scheme II.

The plausibility of such a migration is well supported through the consideration of a molecular model and the fact that the rupture of the carbon-1-to-oxygen bond in the dioxolane ring must involve participation by the oxygen of the pyranose ring. The latter type of participation is clearly involved in all displacement reactions at the anomeric center of sugar structures.

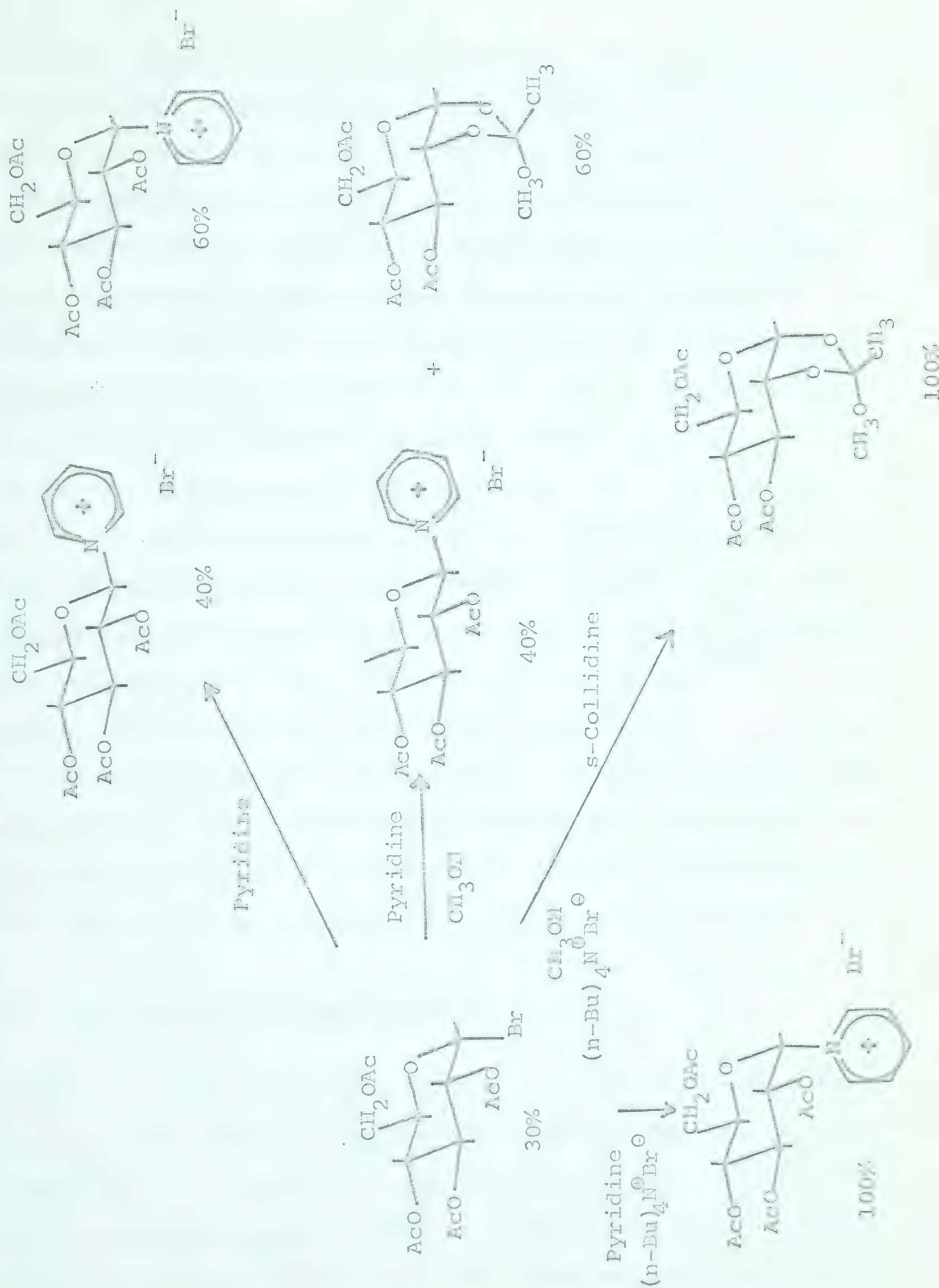
The occurrence of the above migration undoubtedly explains the stereochemical routes of reaction observed in the synthesis

Scheme II

The Mechanism for the Formation of N-(2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl)-pyridinium Bromide (33)



Evidence for 2-Acetoxy Group Participation in the Formation of
N-(2,3,4,6-Tetra-O-acetyl- α -D-glucopyranosyl)-pyridinium Bromide (33)



of 3-carboxamidopyridinium nucleosides (94). The significance of the formation of both anomeric forms in the synthesis of other nucleosides from O-acylated glycosyl halides (100,107,108) is obvious.

It is interesting to note that Fox and Wempen (109), in attempting to rationalize the "trans-rule" in the preparation of nucleosides by the Hilbert-Johnson method, consider the possibility of a double Walden inversion at the anomeric center for a halide with a C1-C2-trans-configuration. The first step may be the inversion of the anomeric center either by the nucleophilic attack of a halide ion, or by the formation of a 1,2-orthoester ion. The inverted halide or the transient carbonium ion may now be attacked by the nitrogen heterocycle with a second Walden inversion to give the 1,2-trans-nucleoside. The latter mechanism involving the carbonium ion was considered the more likely route. In the light of our work it appears that the 1,2-acetoxonium ion rather leads to the formation of the nucleoside with the retention of configuration at the anomeric center. More recently (102) it has been shown that the "trans-rule" is not always obeyed by the Hilbert-Johnson procedure in the condensation of ribopyranosyl halides with pyrimidines.

D. THE FORMATION OF ORTHOESTERS

In the introduction it was pointed out that orthoesters were normally prepared from 1,2-trans-O-acyl-glycosyl halides, although orthoacetates were obtained as side products in some reactions of 1,2-cis-acetohalogenosugars. From our mechanistic interpretation in Scheme II it seemed likely that if a hindered base were used instead of pyridine and bromide ion were added, good yields of

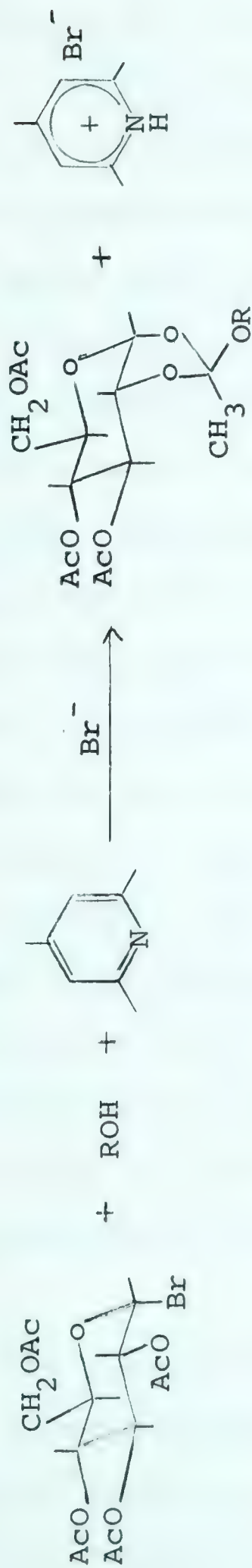
orthoesters should be obtained from 1,2-cis-acylated sugars. α -Acetobromoglucose did not react with s-collidine after 5 days, and s-collidine was therefore chosen as a suitable base.

We obtained approximately 100% yield of the diastereoisomeric orthoesters by this method, but one isomer is normally obtained in large excess. In Table II the percentages of the diastereoisomers, with the chemical shifts of the orthoacetyl signals and the anomeric proton with its coupling constant are given. Lemieux and Cipera (47) concluded that the high degree of partial asymmetric synthesis leaves little doubt that the orthoester is formed by approach of the nucleophile on the side of the positively charged 1,2-acetoxonium ion which is trans to the pyranose ring. Perlin (54) has pointed out from the n.m.r. spectra of diastereoisomeric 1,2-orthoesters in the mannose series that the chemical shifts for the protons of the orthoester ring provide a possible basis for relating the diastereoisomeric orthoacetates. His arguments are equally valid for the 1,2-orthoesters in the glucose series, except that the chemical shift for the 2-proton is not readily observed. Thus of the two diastereoisomers of any 1,2-(alkyl orthoester) the one with the C-methyl signal to lower field in the mixture will be called the "exo"-isomer in this thesis, since it will be assumed that the alkoxy grouping is "exo" to the pyranose ring.

Further evidence in support of this assumption was obtained when it was shown that the presence of the base did not affect the predominant formation of the "exo"-isomer, for example by attack of the alcohol on a transient 1,2-orthoacetyl pyridinium ion with Walden inversion. Also when the isopropyl orthoacetate (35) was

TABLE II

yields in the Preparation of α -D-Glucose 1,2-(Alkyl orthoacetate)Triacetates
and Some of the N.M.R. Spectral Data



Data from the n.m.r. spectra of the crude orthoacetates as prepared above.

Figure	R	% "exo" isomer	C-methyl τ value	Anomeric signal τ value	Spacing (c.p.s.) of anomeric signal	% "endo" isomer	c-methyl τ value
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35*	Me-	89	8.29	4.26	5	11	8.44
37	Et-	85	8.28	4.26	5	15	8.43
39	iPr-	92	8.29	4.34	5	8	8.45
40	t-Bu-	88	8.14	4.29	5	12	8.27
42	Ph-	68	8.23	4.32	5	32	8.42
43*	Ph-	87	8.25	4.32	5	13	8.43

* Not prepared by the standard procedure.

dissolved in 95% ethanol for recrystallization unless care was taken to ensure the medium is not acidic, an exchange took place (55) and the ethyl orthoacetate (34) was formed with the same configuration of the orthoacetate asymmetric centre. Similarly, when β -acetochloroglucose was reacted with methanol in the absence of a base by using silver acetate and dicyclohexylcarbodiimide to remove liberated acid, only the "exo"-methyl 1,2-orthoacetate was formed (Experimental D.1.f.). Therefore the orthoacetates must form by direct attack of methanol on the acetoxonium ion.

The n.m.r. spectra of the crude orthoesters obtained under the standard conditions are shown in Figs. 37, 39, 40, 41, and 42. It was from these spectra that the ratios of the "endo"- to "exo"-isomers were calculated (Table II). Fig. 38 which contains the n.m.r. spectrum of the pure "exo"-ethyl orthoacetate (34) is shown as typical of the pure crystalline "exo"-orthoacetates actually isolated. The n.m.r. spectrum (Fig. 40) of the t-butyl orthoacetate (36) contains a trace of s-collidine as an impurity. The chloroform solution of 36 is too sensitive to acid hydrolysis for the s-collidine to be removed by washing with aqueous acid. The last traces of s-collidine also could not be readily removed from the semi-crystalline mass of 36 by evaporation at 80° in vacuo.

From our conclusions that α -nucleosides can be prepared via transient orthoester-type intermediates which probably rearrange in a 4-center process, we hoped that orthoesters should also rearrange under suitable acidic conditions to α -glucosides. Since initial experiments with the "exo"-orthoesters were not encourag-

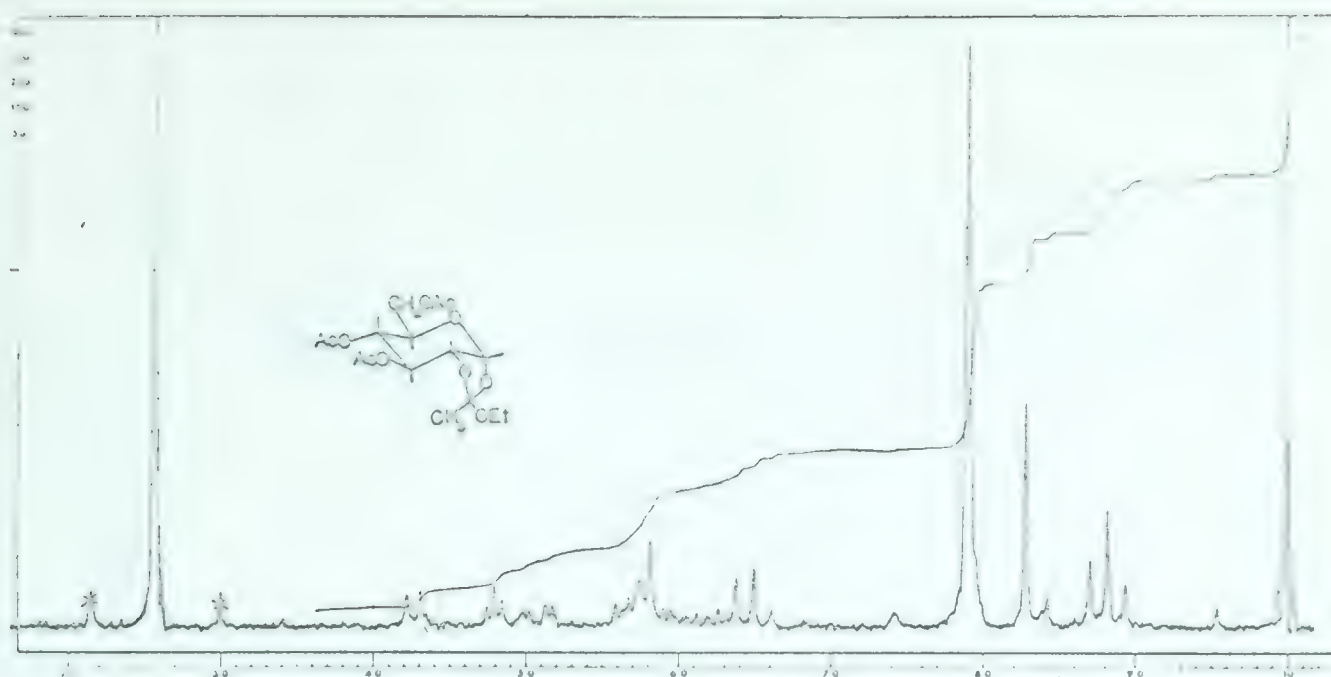


Fig. 37. Crude α -D-Glucopyranose 1,2-(Ethyl Orthoacetate)-3,4,6-triacetate (34) (Chloroform).

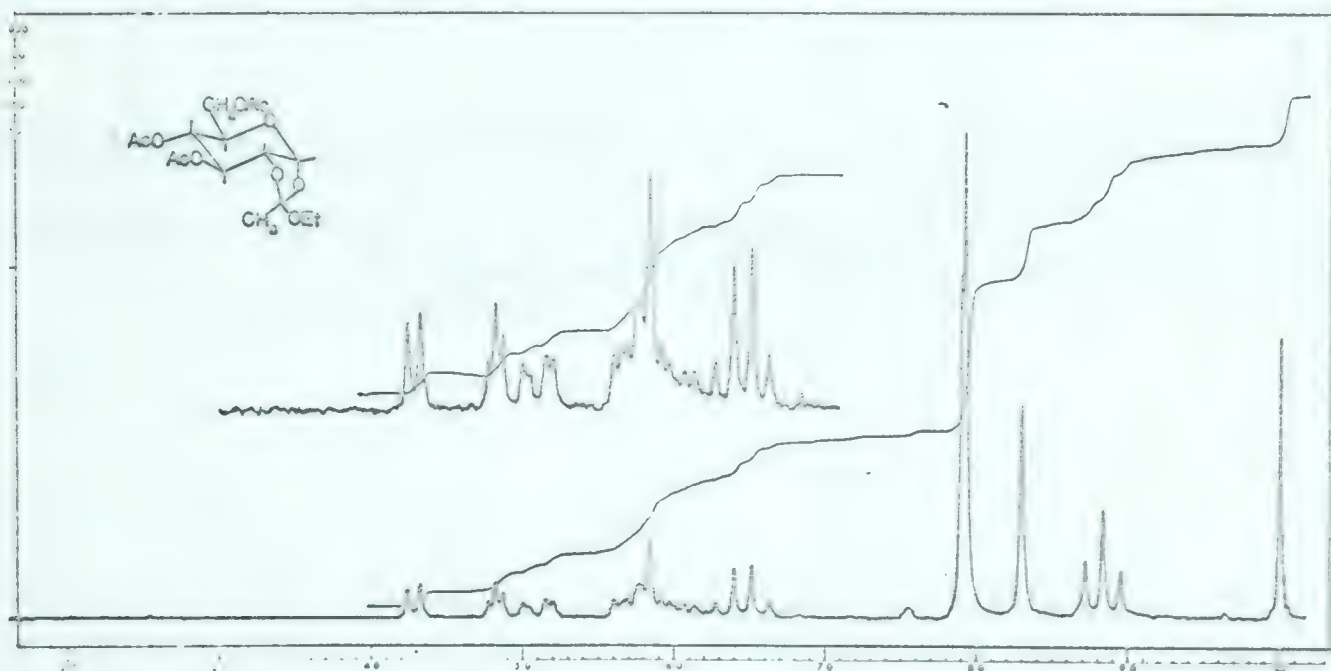


Fig. 38. Pure "Exo" α -D-Glucopyranose 1,2-(Ethyl Orthoacetate)-3,4,6-triacetate (34) (Deuterated Chloroform).

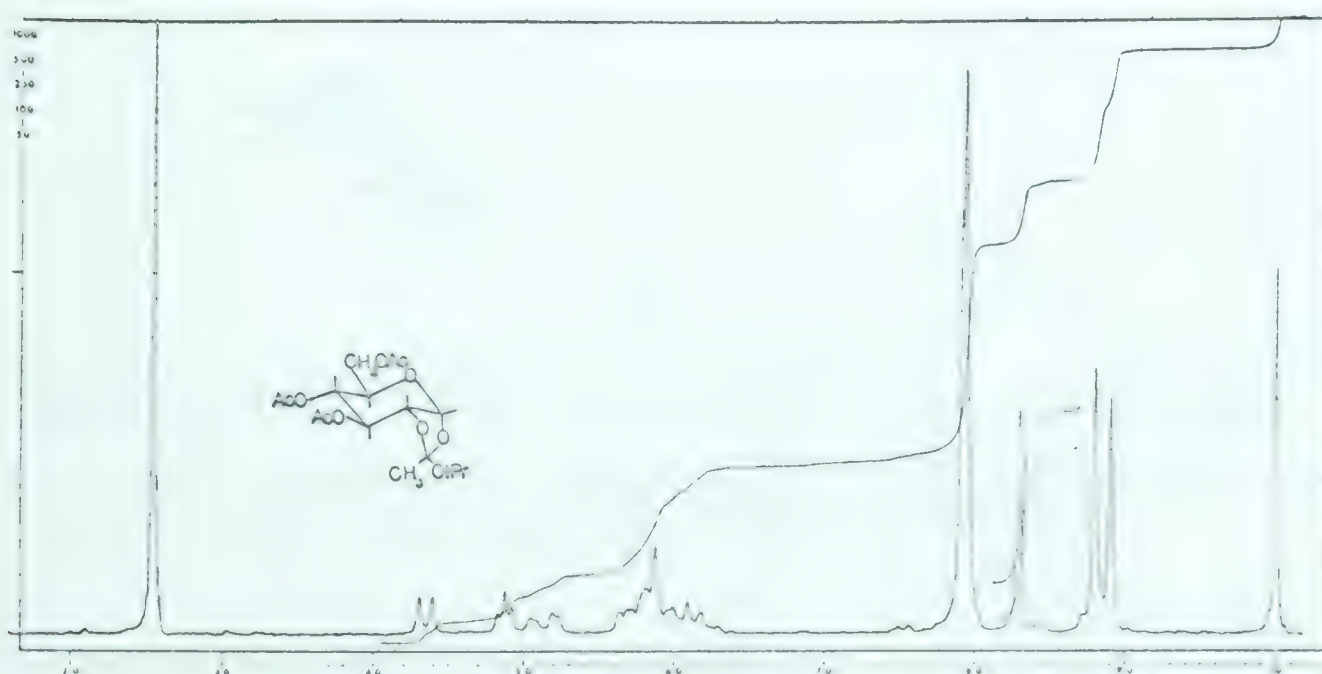


Fig. 39. Crude α -D-Glucopyranose 1,2-(Isopropyl Orthoacetate)-3,4,6-triacetate (35) (Chloroform).

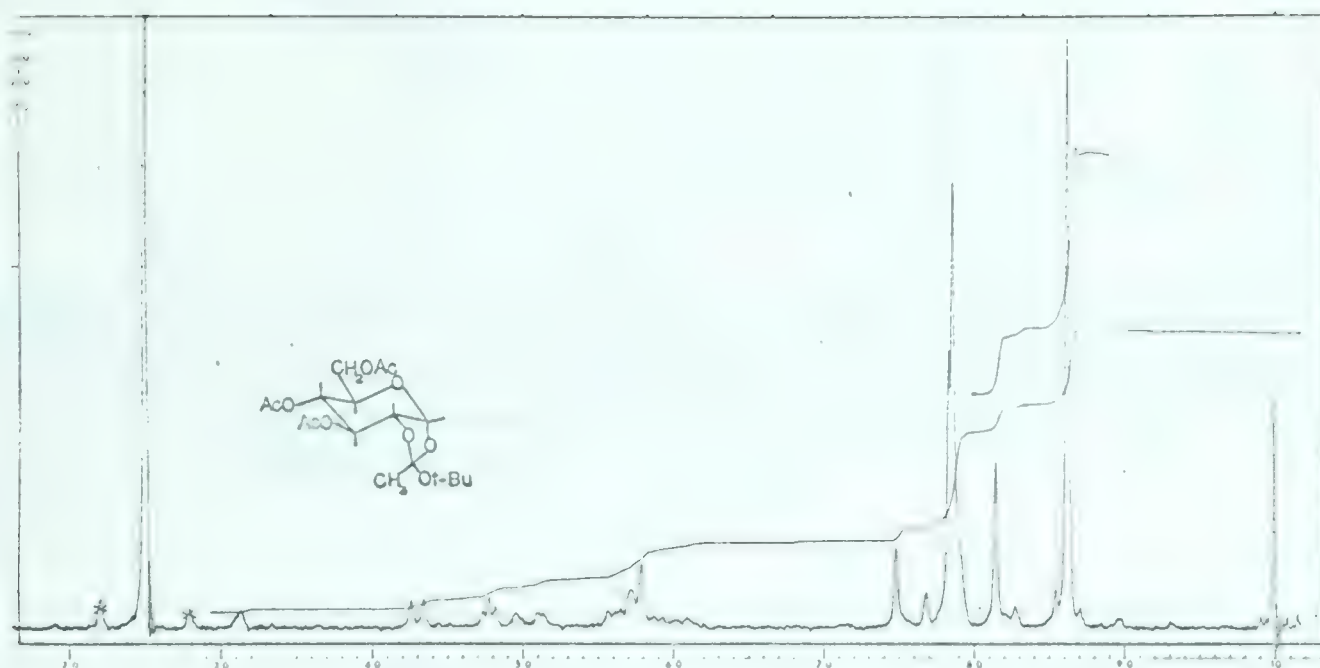


Fig. 40. Crude α -D-Glucopyranose 1,2-(t-Butyl Orthoacetate)-3,4,6-triacetate (36) and a little s-Collidine (Chloroform).



Fig. 41. Crude α -D-Glucopyranose 1,2-(Cyclohexyl Orthoacetate)-3,4,6-triacetate (37) (Chloroform).

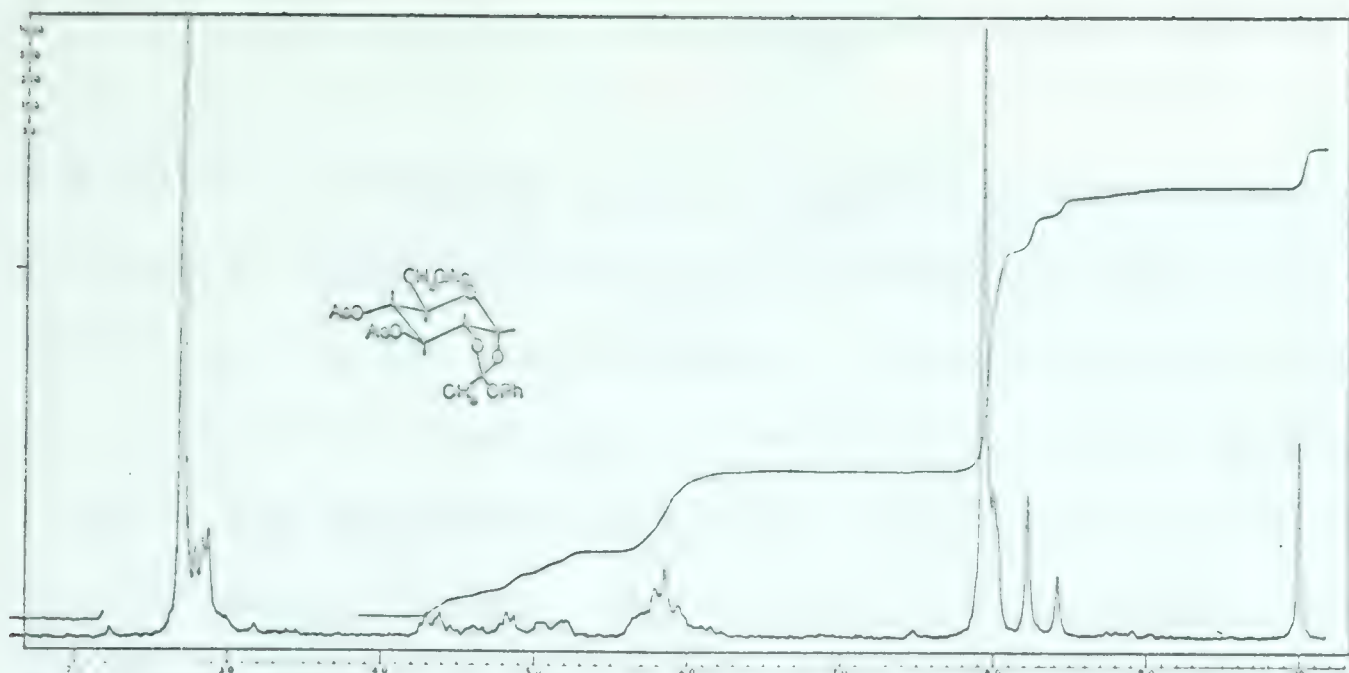


Fig. 42. Crude α -D-Glucopyranose 1,2-(Phenyl Orthoacetate)-3,4,6-triacetate (38), Experimental D.l.e.(i). (Chloroform).

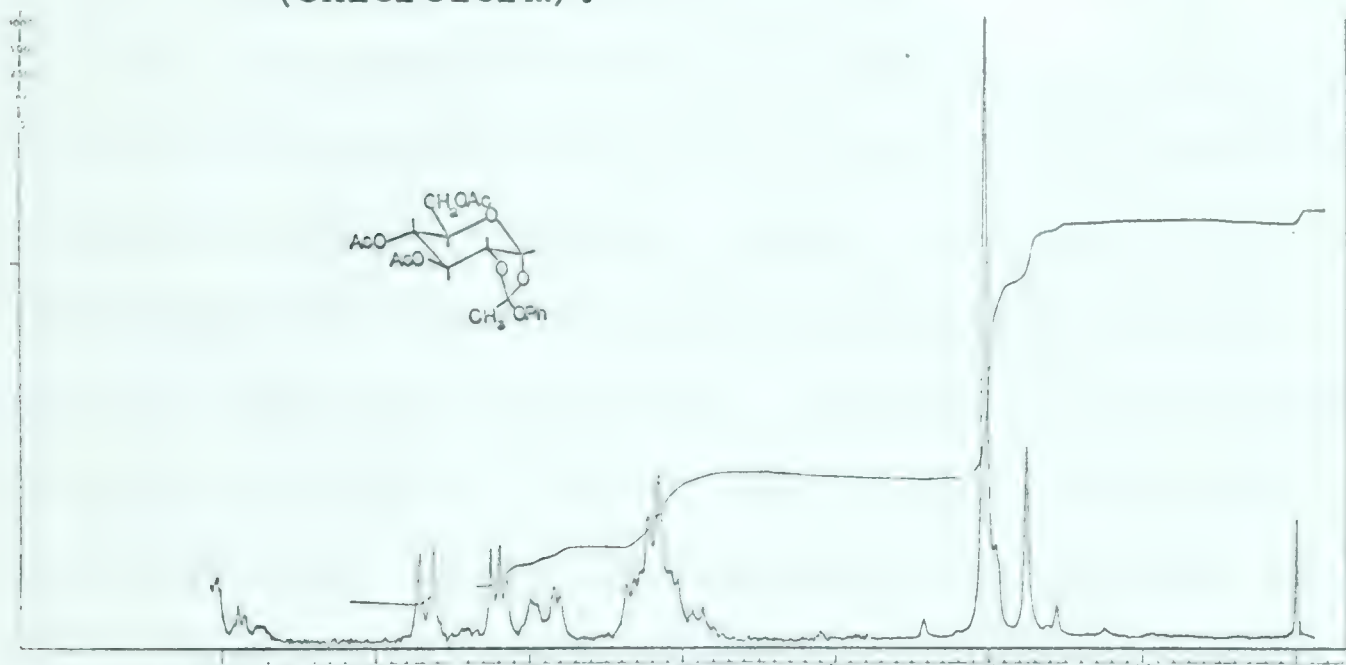


Fig. 43. Crude α -D-Glucopyranose 1,2-(Phenyl Orthoacetate)-3,4,6-triacetate (38), Experimental D.l.e.(ii). (Chloroform).

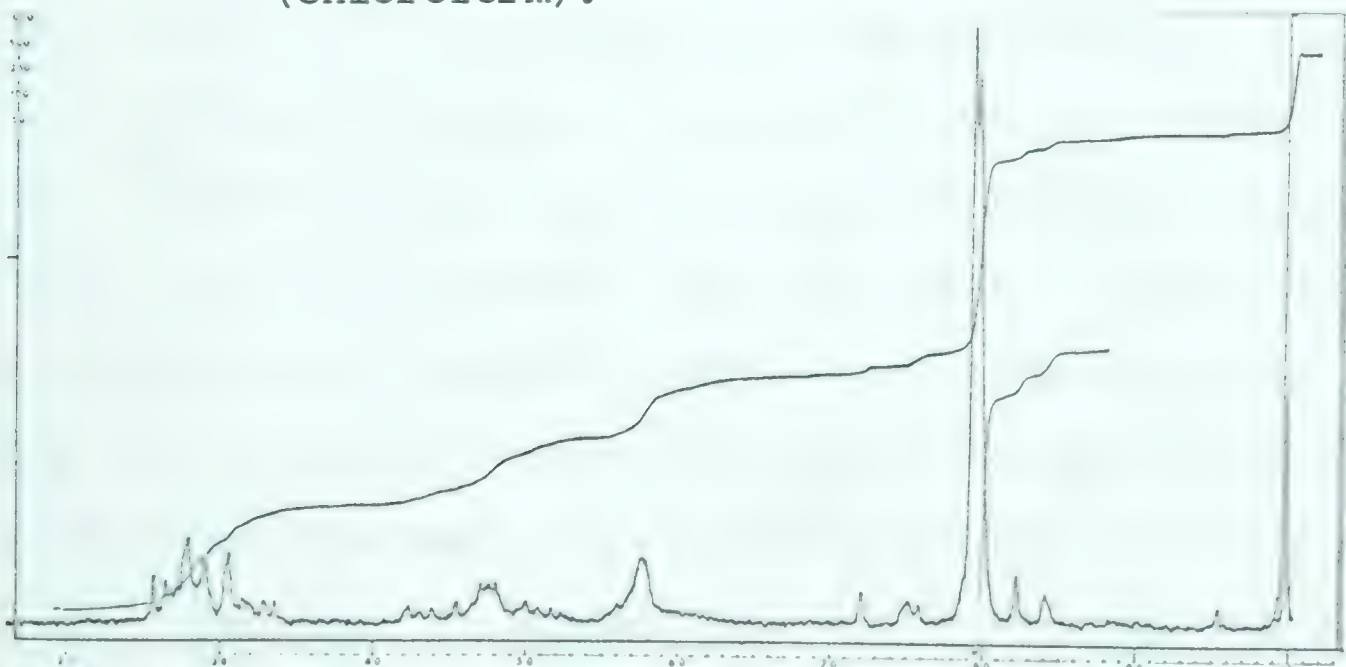


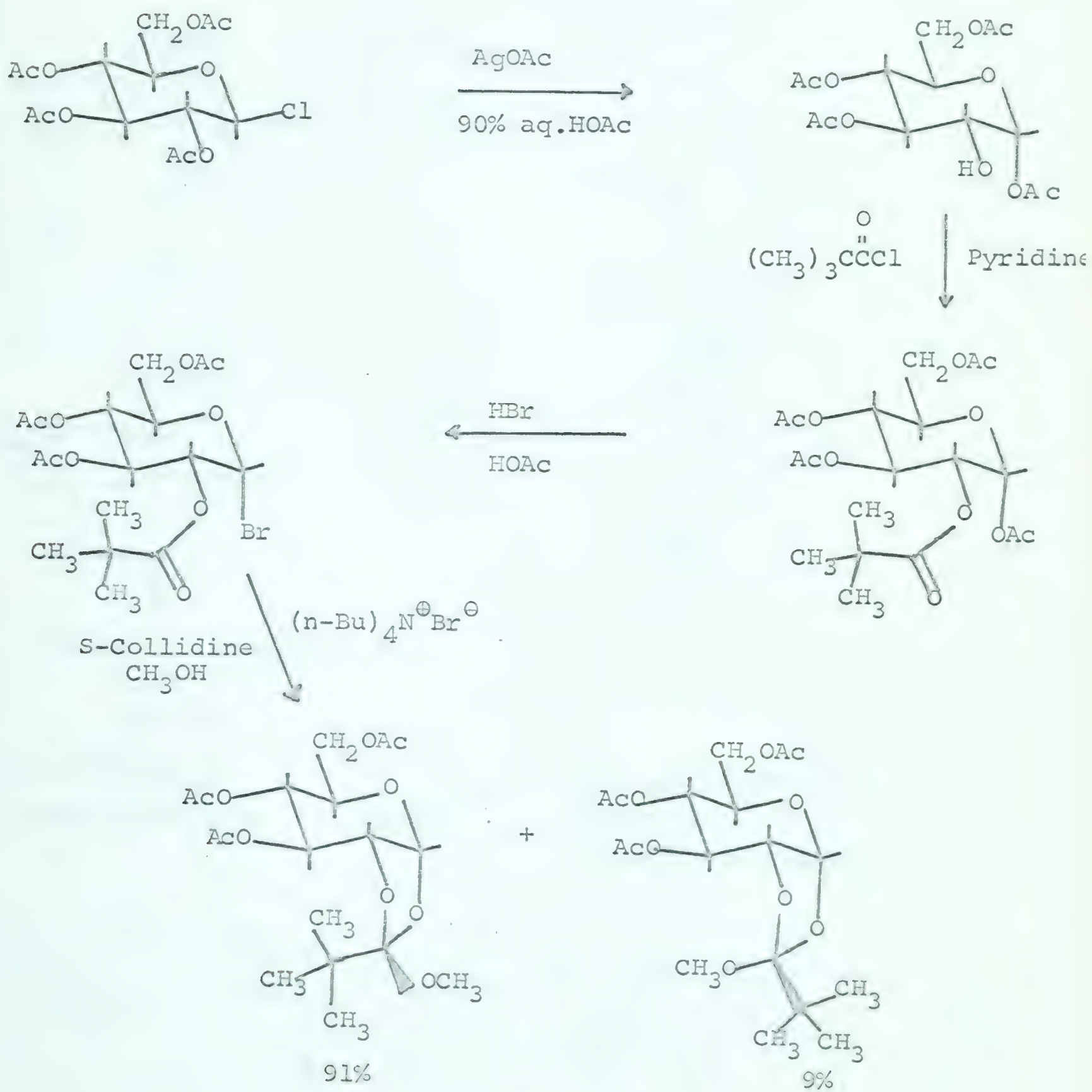
Fig. 44. The Product of the Reaction of Tetra-O-acetyl- α -glucopyranosyl Bromide, Silver Di-s-collidine Fluoroborate and Phenol, Experimental D.l.e. (iii). (Deuterated Chloroform).

ing with a variety of acid catalysts, we decided to attempt to prepare an "endo"-orthoester, in which the configuration would be set up for the rearrangement. Thus the preparation of orthoesters from various other 2-O-acylated groups, namely benzoyl, pivalyl and methoxycarbonyl, was carried out in an attempt to obtain an "endo"-group. Schemes IV and V summarize the reaction sequences which led to the formation of the 1,2-orthopivalates and the 1,2-dimethylorthocarbonate (49).

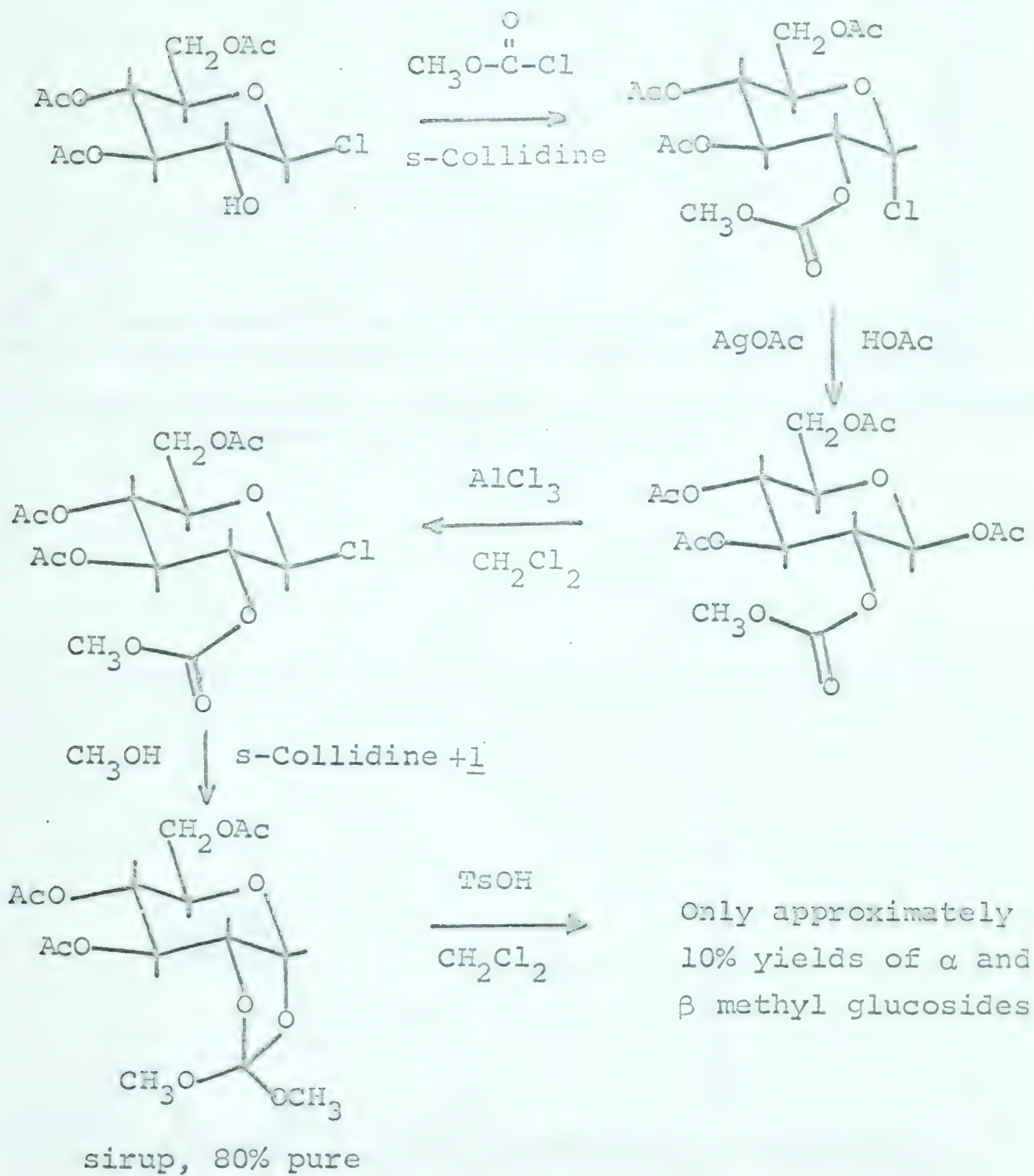
In the preparation of the orthobenzoates and orthopivalates, 1,3,4,6-tetra-O-acetyl- α -D-glucopyranose (17) was acylated with the appropriate acid chloride, and the α -bromide was then formed by treatment with 30% hydrogen bromide in acetic acid. The α -bromide was finally reacted under the standard conditions to form the orthoester desired. Whilst none of the intermediate compounds in the preparation of the orthobenzoate was obtained crystalline, the n.m.r. spectra are unequivocal as to their structure. Thus, the 2-O-benzoate (39) provides an n.m.r. spectrum (Fig. 45) very similar to that of the α -D-glucopyranose pentaacetate. The aromatic protons have too high an intensity, probably due to benzoyl chloride as impurity, and there is a trace of ethanol present. Similarly the n.m.r. spectrum (Fig. 46) of the α -bromide (40) prepared from 39 closely resembles that of α -acetobromoglucose. In preparing the isopropyl orthobenzoate (41) from 40 considerable decomposition was observed as determined from the darkening of the solution. Therefore it was decided not to further investigate orthobenzoates.

Orthopivalates seemed likely on steric grounds to have the

Scheme IV

The Synthetic Route to α -D-Glucopyranose
1,2-Orthopivalates

Scheme V

The Synthetic Routes to α -D-Glucopyranose
1,2-Orthocarbonates

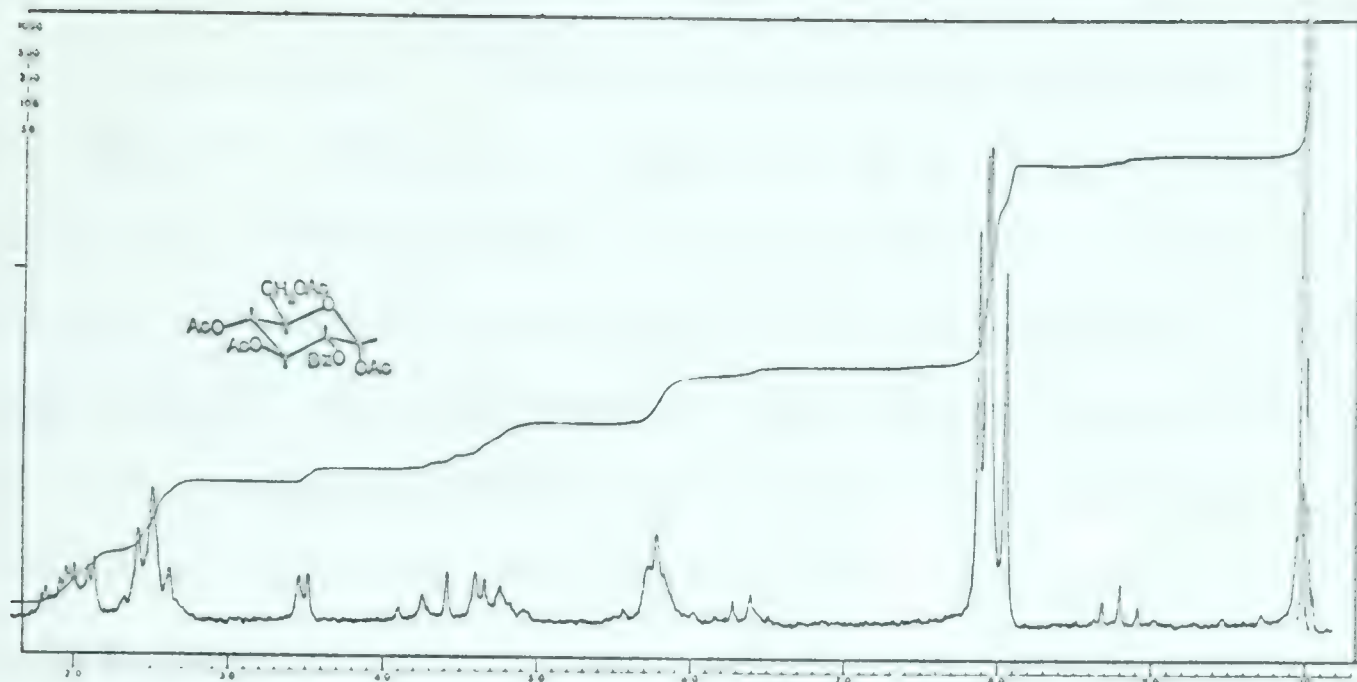


Fig. 45. Impure 1,3,4,6-Tetra-O-acetyl-2-O-benzoyl- α -D-glucopyranose (39) (Deuterated Chloroform).

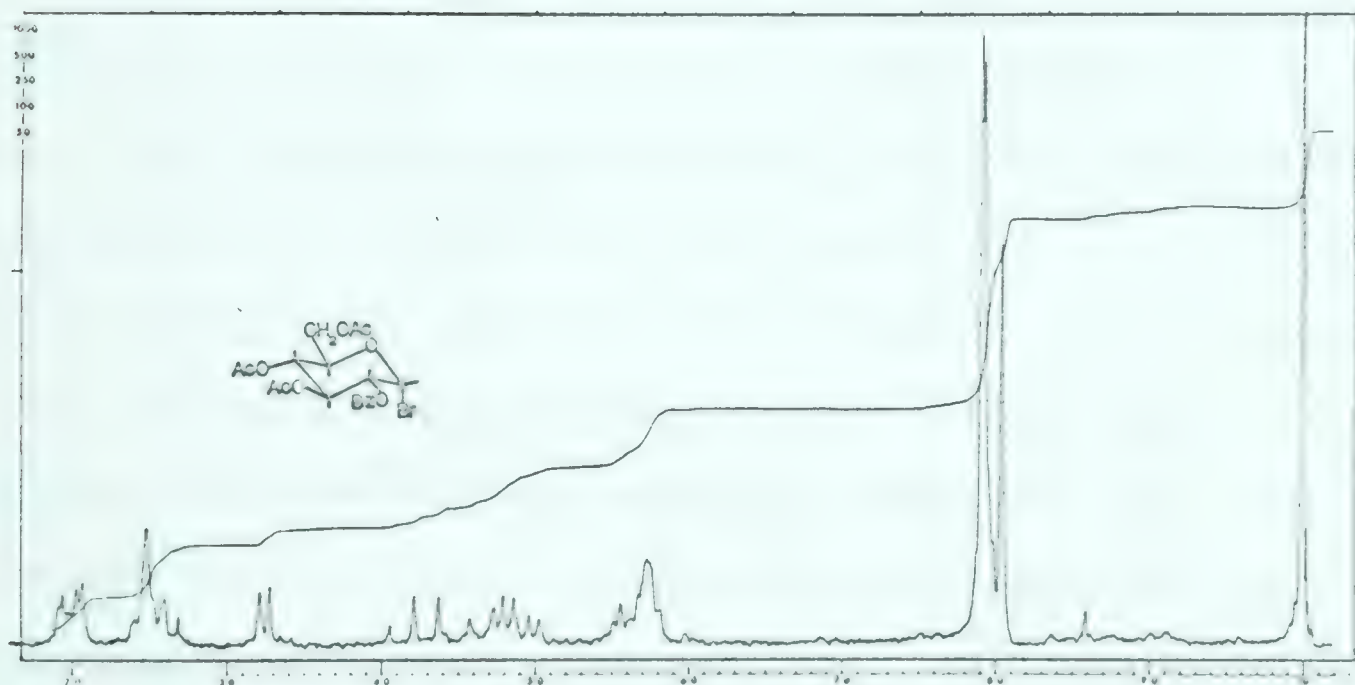


Fig. 46. Syrupy 3,4,6-Tri-O-acetyl-2-O-benzoyl- α -D-glucopyranosyl Bromide (40) (Deuterated Chloroform).

t-butyl grouping exo to the pyranose ring and hence an endo alkoxy group which would be suitably orientated for a rearrangement to an α -glucoside. The tetra-O-acetyl-2-O-pivalyl- α -D-glucopyranose (42) was obtained crystalline, $[\alpha]_D + 93.2^\circ$ (chloroform), and the n.m.r. spectrum (Fig. 47) has a pyranose ring proton structure closely analogous to α -glucopyranose pentaacetate. The α -bromide (43) made by reacting 42 with 30% hydrogen bromide in acetic acid was not obtained crystalline but its structure was confirmed by the n.m.r. spectrum shown in Fig. 48. Except for some fairly marked chemical shifts the ring protons have a similar appearance to that for the 2-O-benzoate α -bromide (40). The remainder of the spectrum is exactly that expected for 3,4,6-tri-O-acetyl-2-O-pivalyl- α -D-glucopyranosyl bromide. The methyl orthopivalate (44) obtained by the standard procedure for preparing orthoesters from the α -bromide (43) has the n.m.r. spectrum shown in Fig. 49. Since the lability of the orthopivalates towards acids was not known, the chloroform solution of 44 was not washed with aqueous acid and hence Fig. 49 contains signals due to N-collidine at about 3.25 τ , 7.55 τ and 7.8 τ . The doublet at 4.17 τ , spacing 5 c.p.s. is undoubtedly that due to the anomeric proton from a comparison with the other orthoesters prepared. The methoxyl peaks at 6.53 τ and 6.71 τ are assigned to the "endo" and "exo" diastereoisomers respectively, assuming that the chemical shifts will be in the same sense as for the corresponding methyl orthoacetates. Thus it is calculated from the intensities that 92% of the "exo"-isomer was formed. The Courtauld models of the two diastereoisomers surprisingly showed that there was not much difference in the

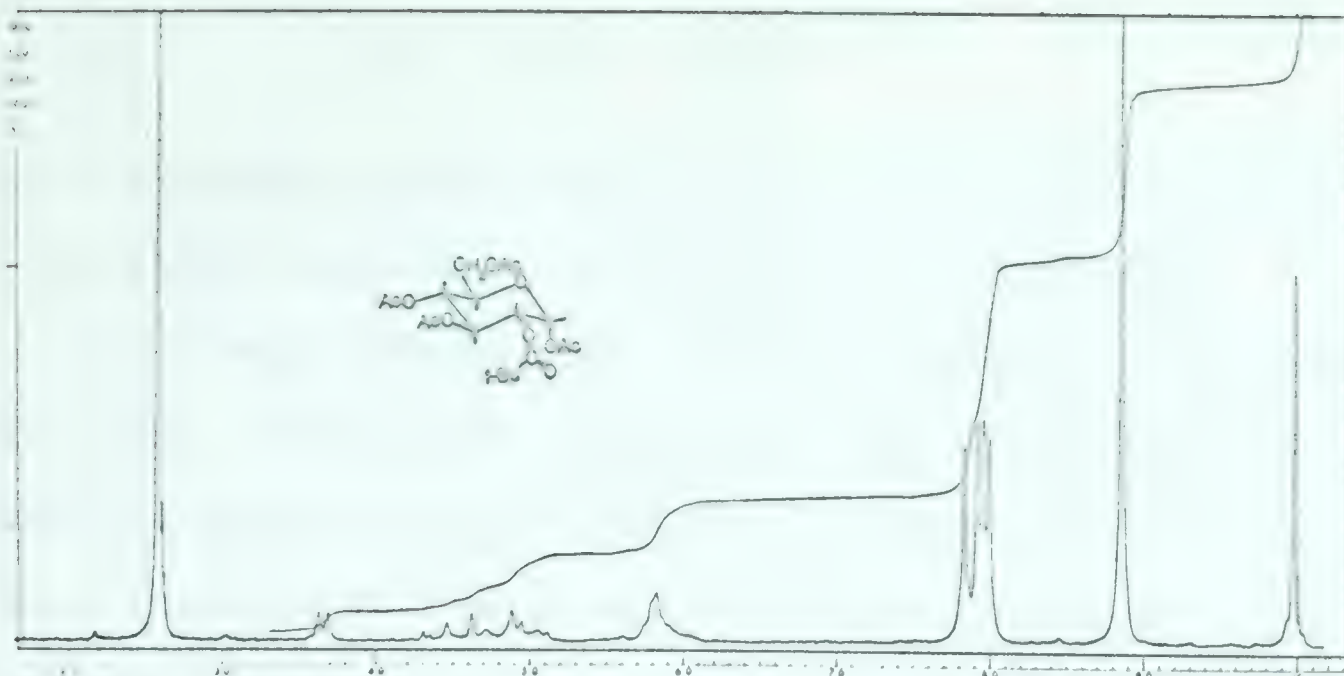


Fig. 47. 1,3,4,6-Tetra-O-acetyl-2-O-pivalyl- α -D-glucopyranose (42) (Chloroform).

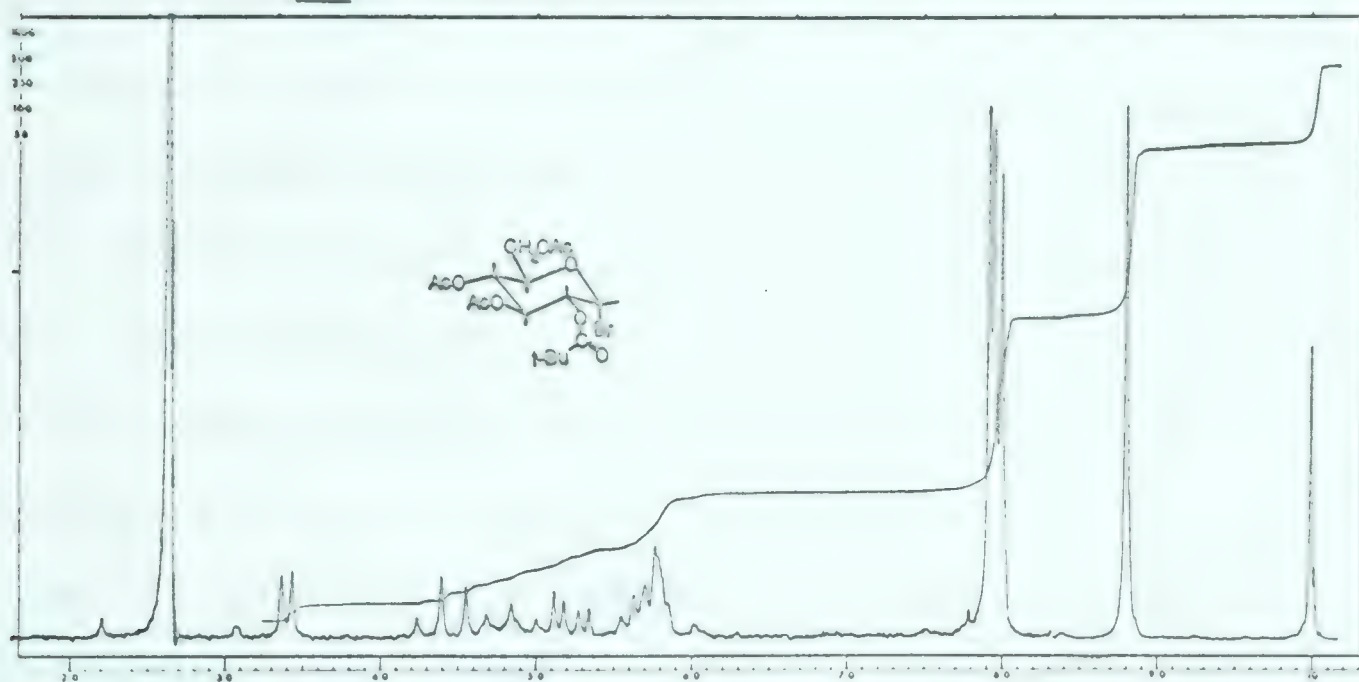


Fig. 48. Syrupy 3,4,6-Tri-O-acetyl-2-O-pivalyl- α -D-glucopyranosyl Bromide (43) (Chloroform). (t-Butyl signal at reduced amplitude).

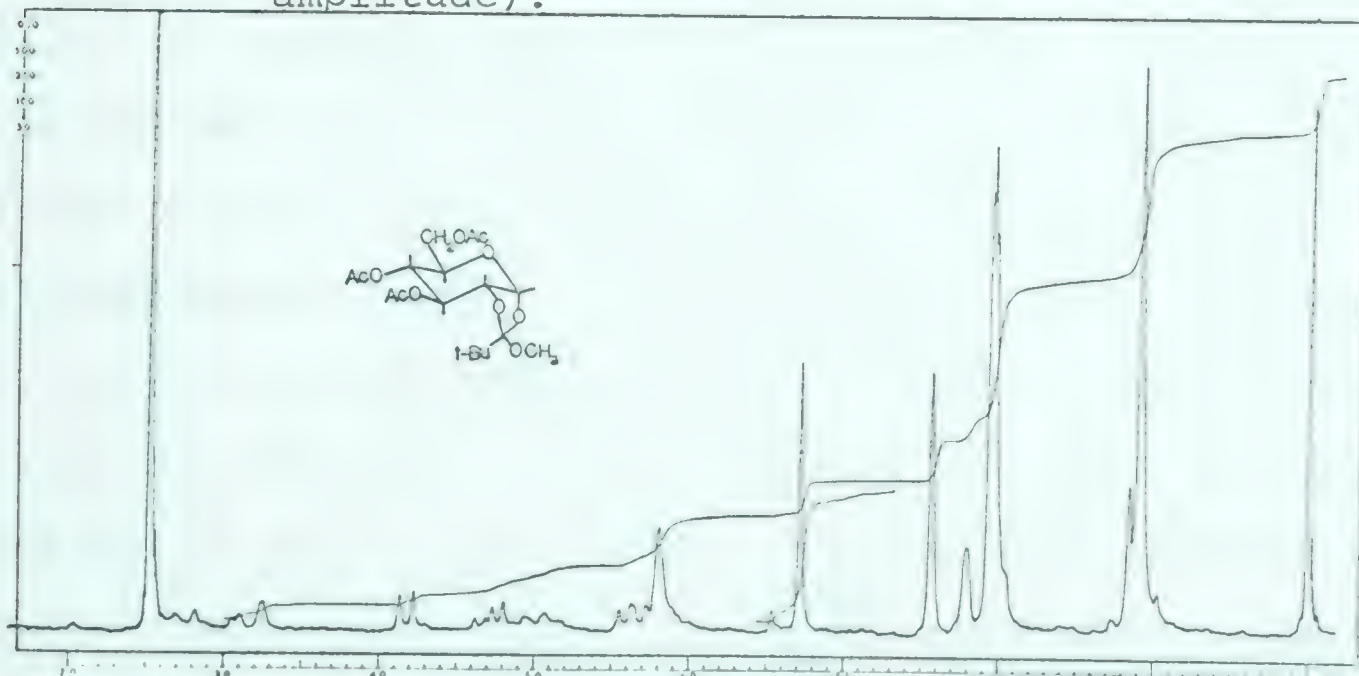


Fig. 49. Syrupy α -D-Glucopyranose 1,2-(Methyl Orthopivalate)-3,4,6-triacetate (44) containing s-Collidine (Chloroform).

steric crowding of the two isomers. Therefore the high proportion of one isomer must arise from electronic factors.

An attempt was therefore made to synthesize an orthocarbonate which must necessarily contain an "endo"-alkoxy group. We succeeded in reacting 3,4,6-tri-O-acetyl- β -D-glucopyranosyl chloride with methylchloroformate in *s*-collidine to form the 2-O-methoxycarbonyl grouping, but in the process the anomeric center was anomerized, as shown by Fig. 50. The anomeric proton at 3.63τ , spacing 3.5 c.p.s. is typical of acylated α -halogenoglucopyranoses. Except for the methoxyl signal at 6.2τ , the rest of the spectrum is typical of α -acetohalogenoglucoses, and thus although the syrup was never crystallized, the structure of 46 was not in doubt. In order to obtain the β -anomer, syrupy 46 was reacted with silver acetate in acetic acid with Walden inversion to give 1,3,4,6-tetra-O-acetyl-2-O-methoxycarbonyl- β -D-glucopyranose (47) in crystalline form, $[\alpha]_D + 13.4^\circ$ (chloroform). The n.m.r. spectrum (Fig. 51) may be readily compared with that of β -glucose pentaacetate. The β -acetate (47) is readily converted to the β -chloride (48), $[\alpha]_D + 5.45^\circ$ in chloroform, by treatment with aluminium chloride in methylene chloride (110), the configuration being retained through neighboring group participation. It is of interest that the methoxycarbonyl group may be expected not to participate as readily as the acetoxyl group since there will be a smaller charge density on the carbonyl group due to the presence of two other electronegative oxygen atoms bound to the carbonyl group. On the other hand any intermediate carbonium ion will be better resonance stabilized than the acetoxonium ion as there are now three oxygen atoms over which to parti-

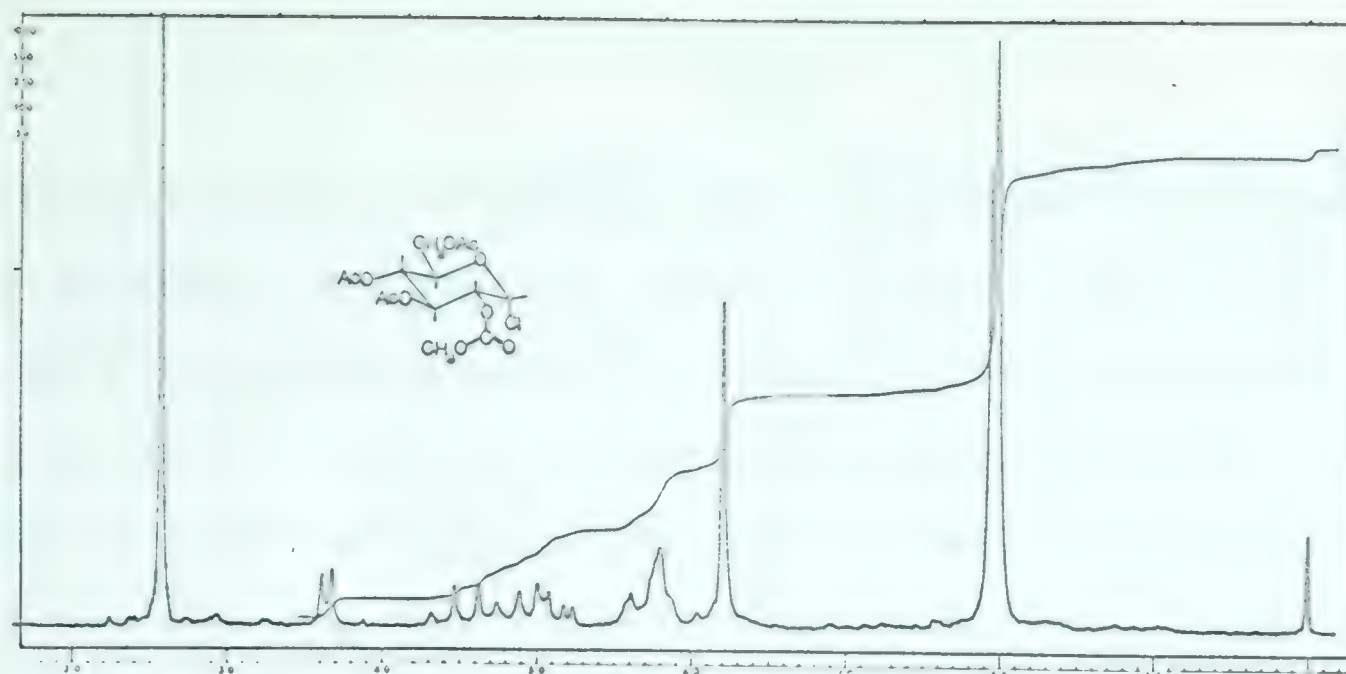


Fig. 50. Syrupy 3,4,6-Tri-O-acetyl-2-O-methoxycarbonyl- α -D-glucopyranosyl Chloride (46) (Chloroform).

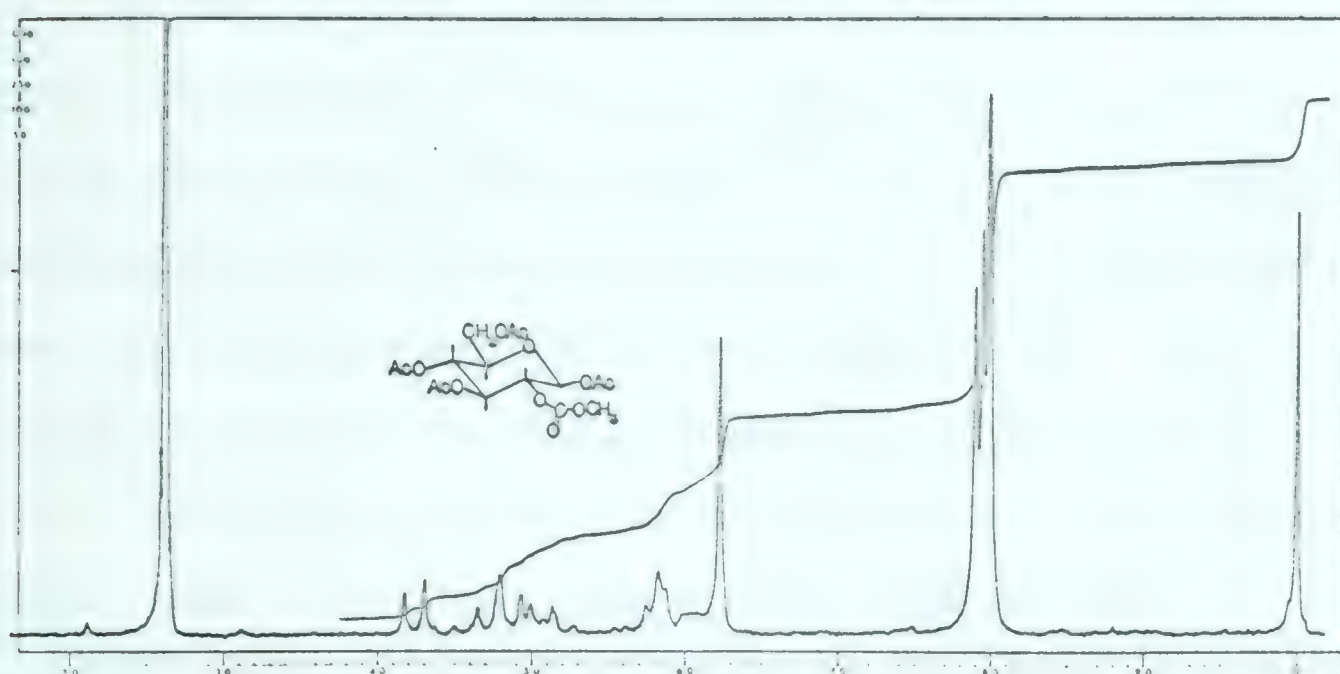


Fig. 51. 1,3,4,6-Tetra-O-acetyl-2-O-methoxycarbonyl- β -D-glucopyranose (47) (Chloroform).

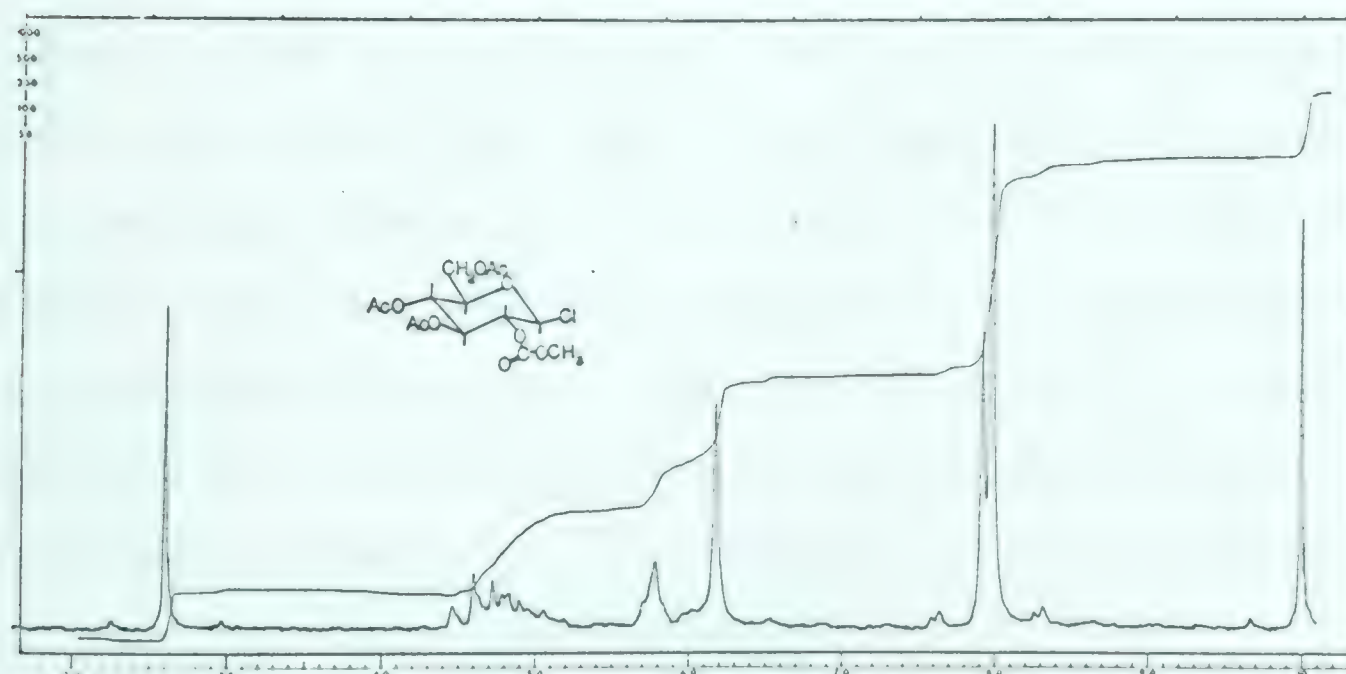


Fig. 52. 3,4,6-Tri-O-acetyl-2-O-methoxycarbonyl- β -D-glucopyranosyl Chloride (48) with Solvated Benzene (Deuterated Chloroform).

ally delocalize the charge. Since the reaction proceeded smoothly in half an hour, the time taken to react β -glucose pentaacetate to give β -acetochloroglucose, it appears that these two effects virtually cancel out. The 2-O-methoxycarbonyl- β -chloride (48) could not be freed entirely of benzene even after prolonged evaporation of the finely ground powder. The n.m.r. spectrum shown in Fig. 52 in deuterated chloroform confirmed the presence of about 1/3 of a mole of benzene per mole of 48, and on this basis the analysis gave good results. The n.m.r. spectrum (Fig. 52) is closely analogous to β -acetochloroglucose. The β -chloride (48) was treated with silver di-*s*-collidine perchlorate (1) and methanol in methylene chloride to form the orthocarbonate (49). The silver salt was added to promote the rapid formation of the cyclic orthocarbonate ion. *s*-Collidine is too hindered to react with the β -chloride (48). The n.m.r. spectrum of the product (Fig. 53) confirms the presence of the dimethyl orthocarbonate in about 85% yield. The anomeric signal at 4.32τ , spacing 5 c.p.s., is typical of that obtained for the orthoacetates. The two methoxyl peaks at 6.55τ and 6.67τ are those of the "exo"- and "endo"-methoxy groups on the dioxalane ring. There is a small signal at 6.25τ typical for methoxycarbonyl and this probably corresponds to a small shoulder on the methoxy signal at 6.55τ . This may be expected to arise from an impurity of a methyl 2-O-methoxycarbonyl-D-glucoside triacetate. It is on this basis that an 85% yield of the orthocarbonate is calculated from the relative intensities.

Attempts to prepare the orthocarbonate from the α -chloride (46) by utilizing the same mechanism as was used to prepare ortho-

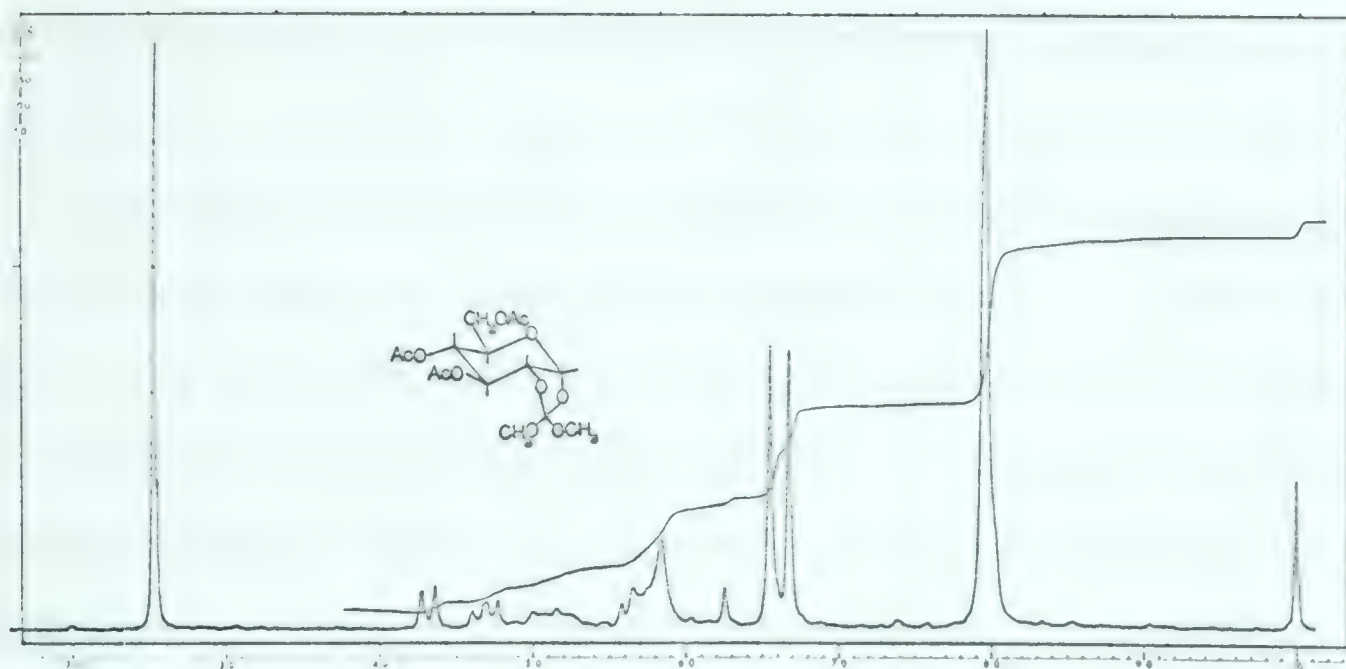


Fig. 53. Impure α -D-Glucopyranose 1,2-(Dimethyl Orthocarbonate)-3,4,6-triacetate (49), Experimental D.4.d.(i). (Chloroform).

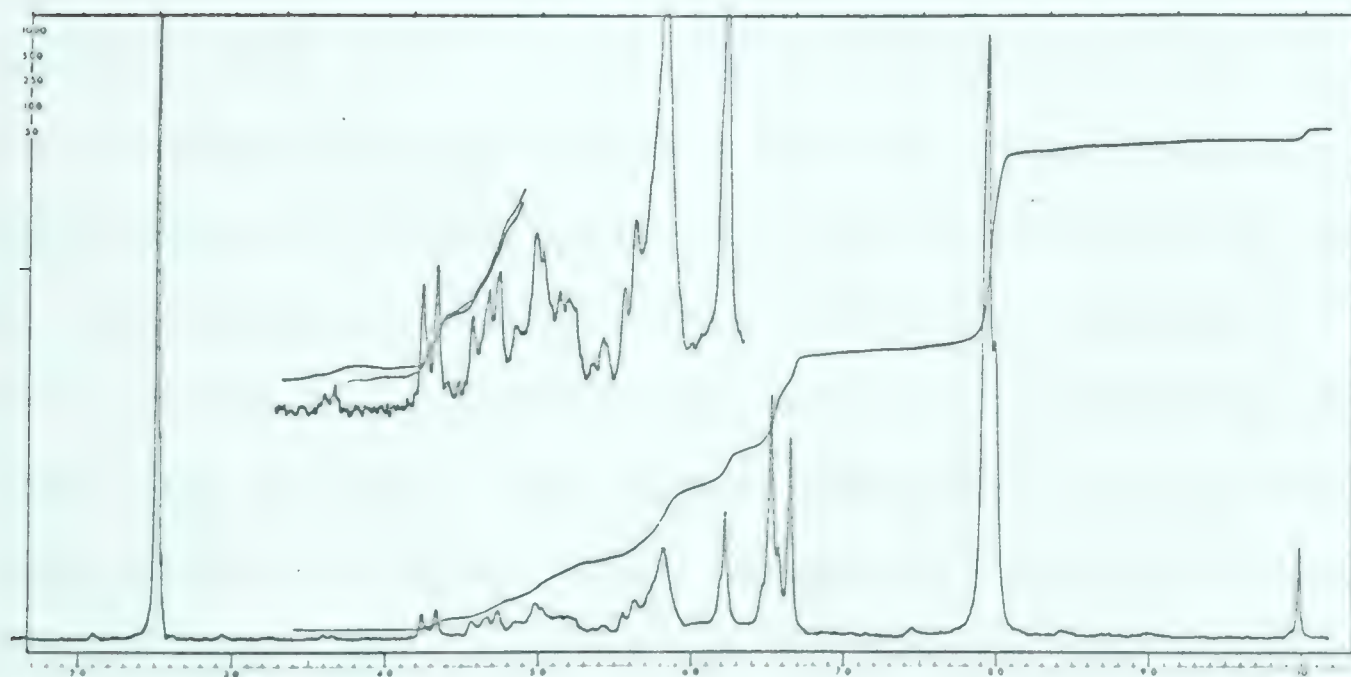


Fig. 54. Impure α -D-Glucopyranose 1,2-(Dimethyl Orthocarbonate)-3,4,6-triacetate (49), Experimental D.4.d.(ii). (Chloroform).

acetates from α -acetobromoglucose, but using chloride ion instead of bromide, were only partially successful, as seen from the n.m.r. spectrum (Fig. 54). The percentage of the orthocarbonate in the mixture is calculated to be 54% by the same method as used above.

The only reference to orthocarbonates of sugars which was found, was that of Lieser and Leckzyck (111). They claimed that when they reacted methyl 6-O-benzoyl-2-O-[(methylthio)-thiocarbonyl]- α -D-glucopyranoside with silver carbonate in methanol, they obtained methyl 6-O-benzoyl-2,4-(dimethyl orthocarbonate)- α -D-glucopyranoside. When the latter compound was treated with methanolic hydrogen chloride, methyl 6-O-benzoyl- α -D-glucopyranoside was isolated and this was taken as evidence of its structure.

It is interesting to note in the preparation of the phenyl orthoester (38) that the standard conditions from α -acetobromoglucose resulted in a relatively large percentage of the "endo"-isomer (32%, Fig. 42). On the other hand when the phenyl β -D-glucoside tetraacetate was expected to form on treatment of α -acetobromoglucose with the silver perchlorate complex (1) and phenol, only the diastereoisomeric orthoesters were produced. In contrast to the above preparation, an only 13% yield of the "endo"-isomer was obtained. The n.m.r. spectrum in chloroform of the crude product isolated in an incomplete reaction of α -acetobromoglucose with isopropanol in the presence of the silver perchlorate complex (1) possessed signals that could be assigned only to the isopropyl orthoacetate (35) and starting material. There was a sharp signal at 8.28τ , typical of the orthoacetyl group of 35, and a doublet of spacing 6 c.p.s. at 8.83τ with double the intensity

(see Fig. 39). Thus since no glucoside was formed with the silver perchlorate complex (1), α -acetobromoglucose must dissociate to bromide and the 1,2-acetoxonium ions before the phenol attacks. Significantly, when silver di-s-collidine fluoroborate was substituted for 1, a 10% yield of the phenyl tetra-O-acetyl- β -D-glucopyranoside was isolated and the n.m.r. spectrum of the product, Fig. 44, indicated an only 20% yield of the "exo"-orthoacetate. Assuming that the spinning side band at 8.41τ corresponds to the signal for the "endo"-orthoacetyl group, the total yield of the orthoacetate was less than 40%. In fact, the spectrum of the product resembles that of phenyl tetra-O-acetyl- β -D-glucopyranoside. Although the phenyl β -D-glucoside tetraacetate was isolated in low yield, when ethanol was substituted for phenol (Experimental D.1.e.(iv).), a 50% yield of the crystalline ethyl β -D-glucopyranoside tetraacetate was isolated, and the n.m.r. spectrum of the crude product was almost identical to ethyl β -D-glucoside tetraacetate with s-collidine as an impurity.

Thus the anion of the silver salt has a profound effect on the course of the reaction, even though an essentially homogeneous reaction since the silver salts were fairly soluble in the solvents used. The reasons for this effect, whilst not properly understood, must be due to the relative stability of ion pairs which are formed in the reaction. Evidently, the di-s-collidine silver fluoroborate complex shows considerable promise as a reagent for the preparation of glycosides.

It was mentioned earlier that Fischer and Raske (69) added α -acetobromoglucose to pyridine containing phenol to prepare the

β -pyridinium glucoside (26). Although they did not comment on the reason for adding phenol, in view of our results it could be anticipated that the phenol would eliminate the formation of the α -pyridinium compound (33) by trapping any 1,2-acetoxonium ion. Thus the isolation of 26 would be straightforward and likely this accounted for their success.

E. ACID CATALYSED REACTION OF ORTHOESTERS GIVING α -GLUCOSIDES

As mentioned in Section D, a reasonable mechanism for the formation of α -glucosides from 1,2-orthoesters can be postulated under acidic conditions. Strictly anhydrous conditions must be used since it is known (47) that the acetoxonium ion will scavenge trace amounts of water in acetic acid. In preliminary experiments a variety of solvents (chloroform, methylene chloride, acetonitrile and benzene) and acid catalysts (picric acid, p-toluenesulphonic acid, hydrogen bromide, borontrifluoride etherate, tri-n-butyl boron, tetraphenyl tin etc.) were used. It was found that unless an alcohol were present very little glucoside was formed as judged from the n.m.r. spectra of the crude reaction products. When an alcohol was present α -glucosides were isolated by Celite column chromatography of the deacetylated syrup.

When the t-butyl orthoacetate (36) was treated with half a mole excess of isopropanol in methylene chloride with picric acid, 10 mg, as the catalyst (about 1/40th the molar concentration of the orthoester, 36), an initial very rapid rise in rotation was observed, and the rotation then rose more slowly over the next 29 hours. The n.m.r. spectrum of a sample of the reaction mixture

indicated that 42% of an orthoester was unreacted and it corresponded to the isopropyl orthoacetate (35) not the t-butyl orthoacetate (36). This was confirmed by the actual isolation of 35 (Experimental E.1.c.(ii)). A further 10 mg of picric acid was added, and the rate of the rise in rotation increased although not as markedly as initially. Finally, when the rotation was constant, a further 13 mg of picric acid was added but the rotation only rose slightly. The n.m.r. spectrum had no C-methyl group signals attributable to orthoacetates. Deacetylation and Celite chromatography lead to the isolation of the t-butyl α -D-glucopyranoside in 47% yield. A slower moving component of $R_G = 3.1$ was thought to be due to isopropyl glucosides. The surprisingly high yield of the t-butyl glucoside was unexpected since exchange of alkoxy groups had occurred. Therefore it seemed likely that it was the free alcohol that gave rise to the α -glucoside and not some rearrangement of the orthoester. Column chromatography is a tedious and time consuming operation, besides not being a good analytical tool, and therefore the trimethylsilyl (tms) derivatives (72) of the deacetylated products were prepared for analysis by g.-l.p.c.

The methyl, ethyl, isopropyl and t-butyl α - and β -D-glucopyranoside tetraacetates were prepared by standard methods. Known quantities of the glucosides were added to known quantities of pentaerythritol tetraacetate, chosen as the internal standard, and together they were deacetylated in triethylamine, methanol and water. The syrupy product was trimethylsilylated under standard conditions, and the pyridine solution of the tms derivatives was analysed by g.-l.p.c. Hence a correlation could be made between

the areas of the peaks for the glucoside tms derivatives on the chromatogram and that of the pentaerythritol tms derivatives. Varying the concentration and the relative quantities of the pentaerythritol tetraacetate and the acetylated glucosides still gave good analytical results. The main source of error was the instability of the base line which led to a maximum 10% error in the estimation of the integrated areas of the peaks on the chromatogram. In the analysis of the actual reaction products, as already discussed in the Experimental, Section E., glucose was found to be present in small yield. This could be due to trace amounts of water in the reaction mixture or due to a small amount of unreacted orthoester. When the orthoesters were subjected to the standard reaction conditions described in the Experimental without the addition of alcohol, and immediately evaporated to a syrup which was dissolved in methanol and water prior to adding the triethylamine to deacetylate, it was found that only α - and β -D-glucose were detected in the standard method of analysis by g.-l.p.c. Thus the orthoester is rapidly hydrolysed, when dissolved under acidic conditions in aqueous methanol, to products which deacetylate to give glucose. Thus any unreacted orthoester will analyse as glucose in the standard procedure used.

Although the tms derivative of α -D-glucose always coincided with the derivatives of the simple alkyl α -D-glucosides considered on analysis by g.-l.p.c., the β -D-glucose tms derivative had a longer retention time than the tms derivatives of alkyl β -D-glucosides. Hence since the ratio of α - to β -D-glucose was constant under the standard conditions employed, the yields of the α - and

β -glucosides as well as that of glucose could still be calculated. The tms derivatives of the methyl glucosides were not readily separated on the columns tried out. Also the tms derivatives of glucosides with the same anomeric configuration but different aglucones were not separated. Unfortunately therefore, for successful analysis the alkoxy group for the orthoester had to correspond to the alcohol used.

The three orthoesters, the ethyl (34), isopropyl (35) and t-butyl (36), were reacted under standard conditions, 0.4 M in the orthoester, 0.08 M in p-toluenesulphonic acid, 0.4 M in the corresponding alcohol in methylene chloride as the solvent. The products of the reaction from 34 and 35 are given in Table IV, and the change in the observed rotation in Diag. 3. As seen good yields of the α -glucoside were obtained. The effect of increasing the molarity of the alcohol did not significantly alter the yields. The effect of omitting the alcohol leads to a drastic reduction in yield (Table IV) and this is discussed later. An examination of the volatile components of the reaction showed that ethyl acetate is formed virtually quantitatively from 34 and isopropyl acetate from 35 under the standard conditions. Thus the product of the reaction must have lost an acetyl group. The n.m.r. spectrum (Fig. 55) of the crude product from the reaction of isopropyl orthoacetate (35) under the standard conditions showed a signal pattern for the isopropyl group which was quite different from that of the isopropyl α - and β -D-glucopyranoside tetraacetates. The chemical shifts of the two methyl signals, which have spacings of 6 c.p.s. due to coupling with the secondary proton

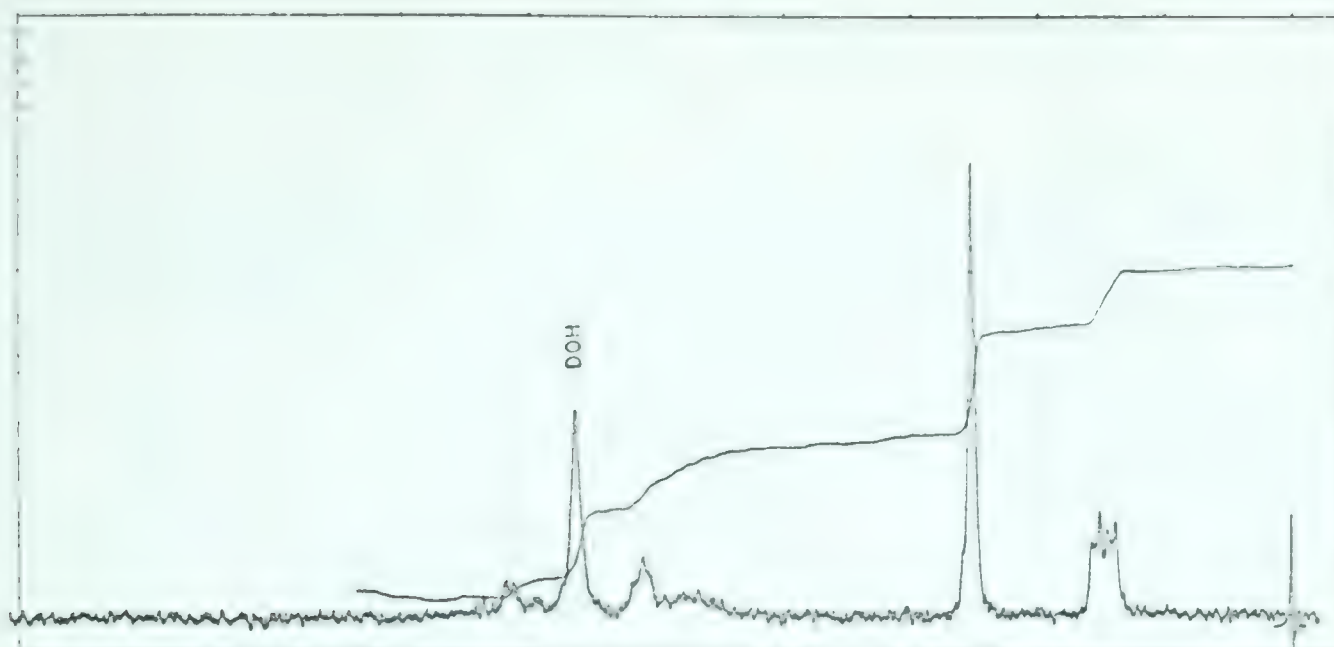


Fig. 55. Impure Isopropyl 3,4,6-Tri-O-acetyl- α -D-glucopyranoside, Experimental E.l.b.(i). (Deuterium Oxide).

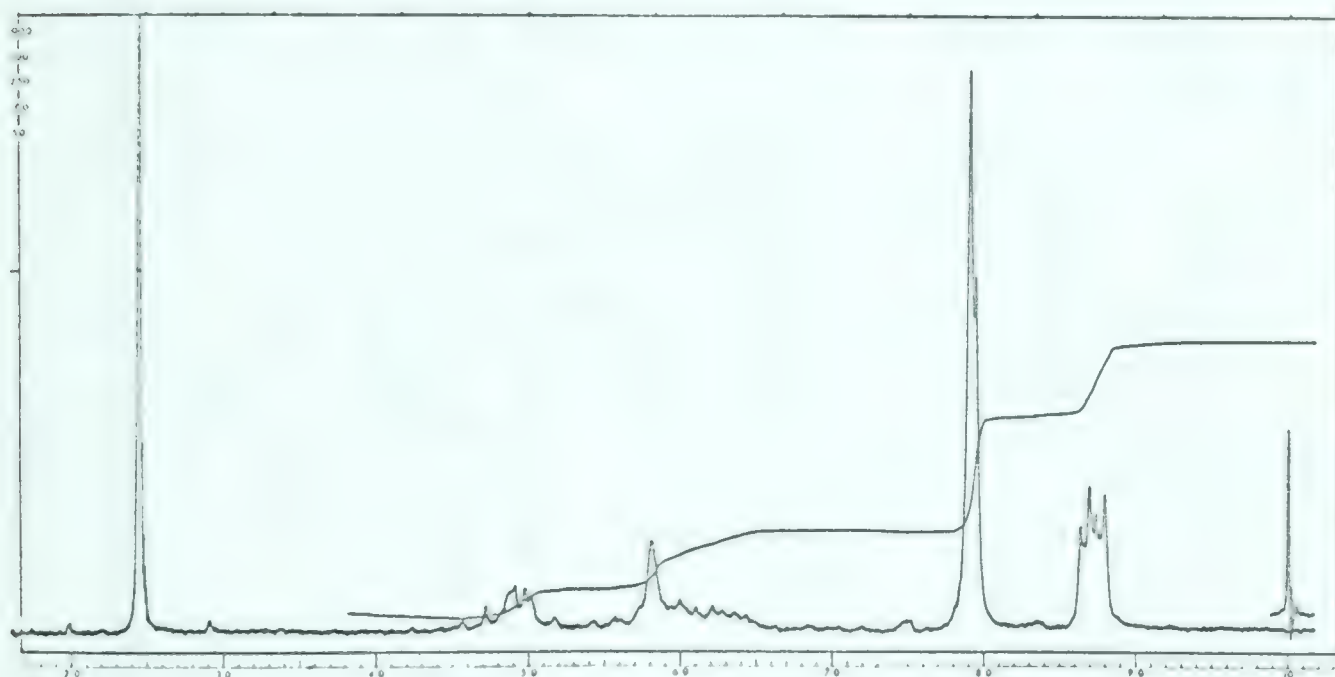


Fig. 56. As for Fig. 55 (Chloroform).

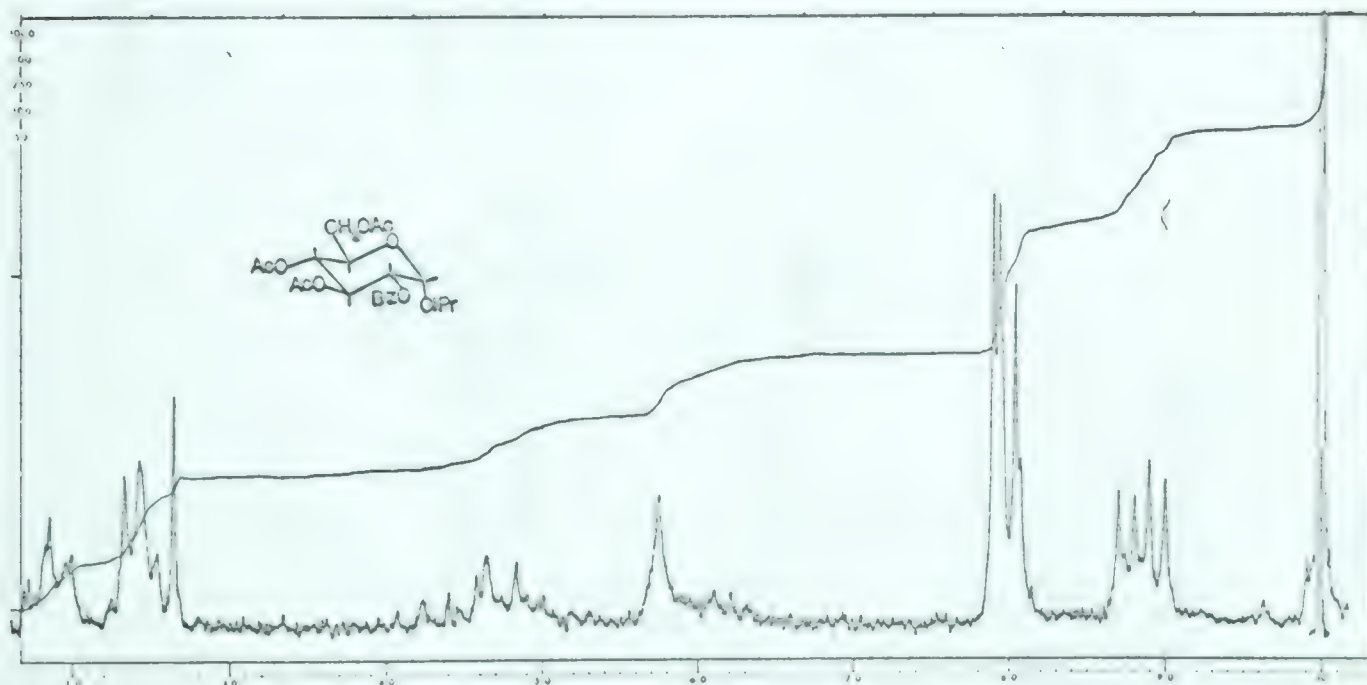


Fig. 57. Impure Isopropyl 3,4,6-Tri-O-acetyl-2-O-benzoyl- α -D-glucopyranoside, Experimental E.l.b.(i). (Deuterated Chloroform).

TABLE IV
 α -Glucoside Formation from Orthoesters

R	Molarity of ROH	Glucosides		% Yields	
		α	β		Glucose
$-\text{CH}_2-\text{CH}_3$ (34)	0.4	53	32		11
$-\text{CH}(\text{CH}_3)_2$ (35)	5.5	69	20		15
	0.4	72	21		6
	0	21	5		27

t-Butyl orthoester + 1.4 Isopropanol $\xrightarrow[\text{CH}_2\text{Cl}_2]{\text{Picric Acid}}$ 47% isolated yield of t-Butyl α -D-glucoside

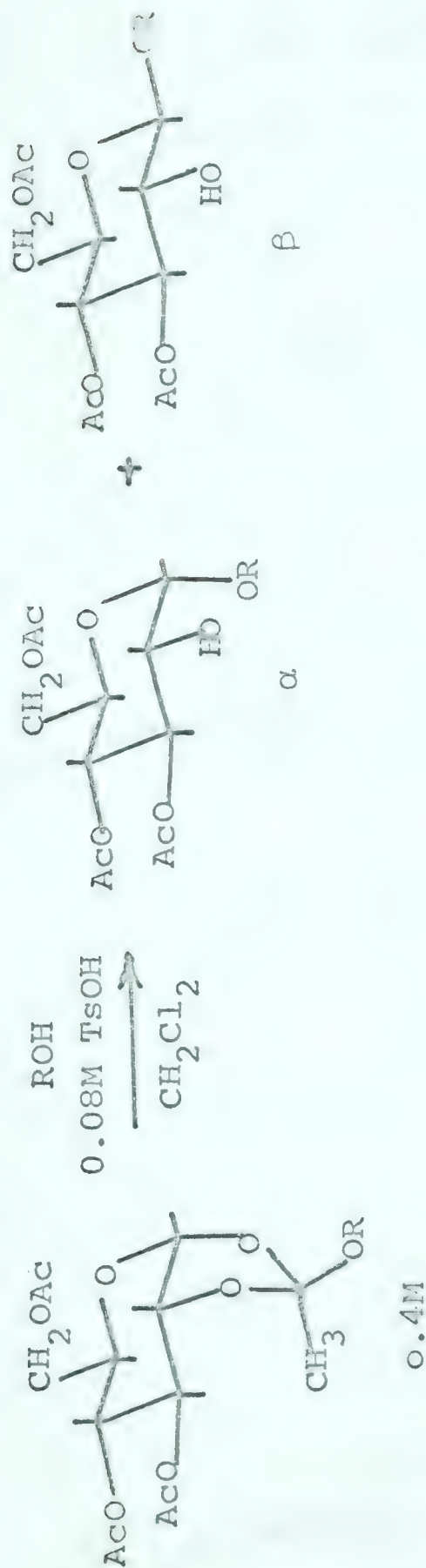
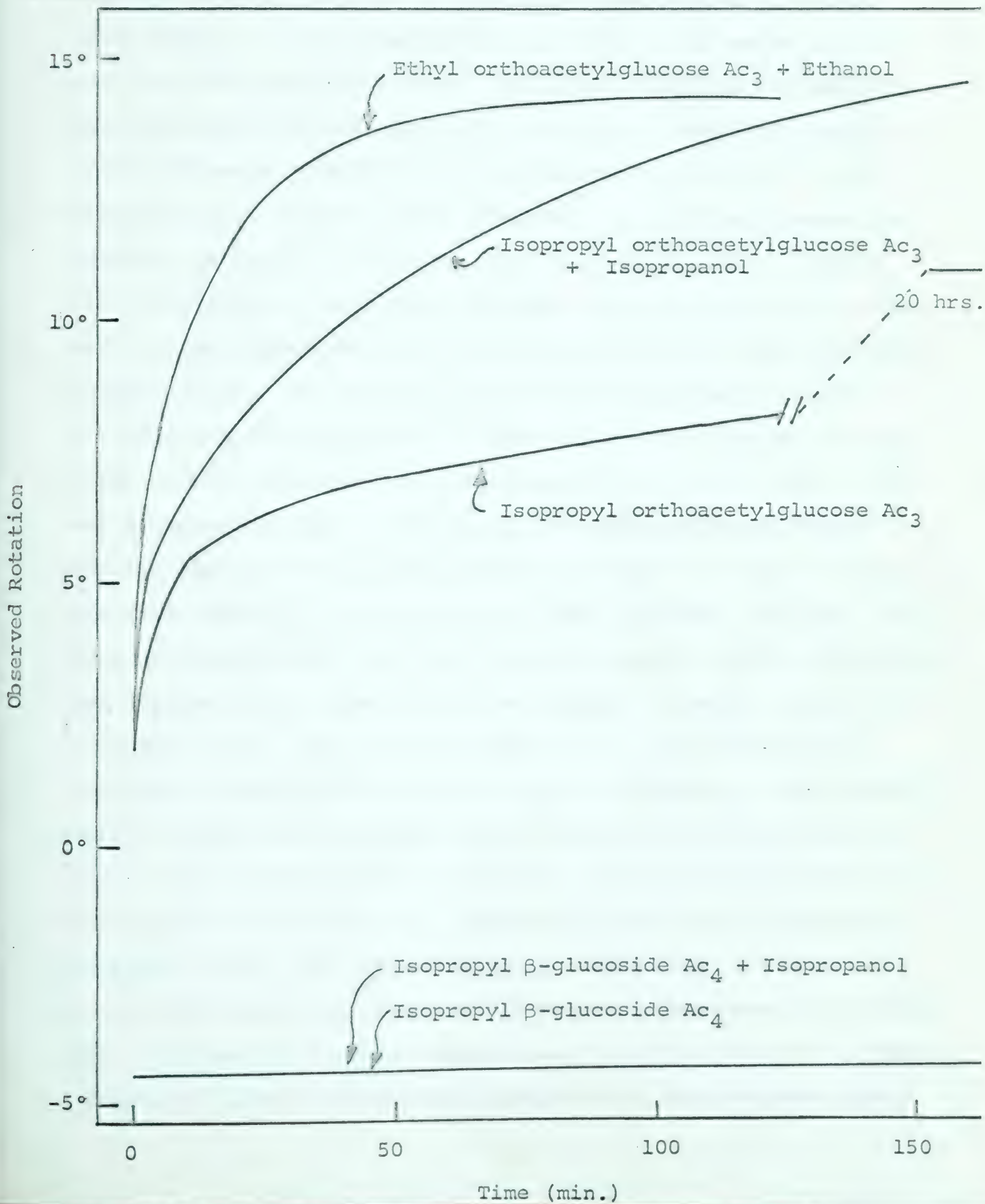


DIAGRAM 3

Polarimetric Rates of Reaction of 0.4M Solutions of Orthoesters, Alcohols and β -Glucosides in Methylene Chloride, 0.08M in p-Toluenesulphonic Acid



are very sensitive to their environment (112). Thus whilst the isopropyl orthoacetate has in its n.m.r. spectrum (Fig. 39) a clean doublet at 8.85τ spacing 6 c.p.s. (i.e. both methyl groups have identical chemical shifts), the n.m.r. spectrum of isopropyl α -D-glucopyranoside tetraacetate contains a triplet, spacing 6 c.p.s., centered at 8.80τ (i.e. a difference of 6 c.p.s. in the methyl chemical shifts). The n.m.r. spectrum of the β -anomer has a quartet centered at 8.84τ but with the central pair of peaks scarcely resolved. Thus the four peaks in Fig. 55 indicated a new compound, presumably mainly isopropyl 3,4,6-tri-O-acetyl- α -D-glucopyranoside, since the product on deacetylation contained 70% of isopropyl α -D-glucopyranoside. This was confirmed by acetylation of the product to give a crude product with an n.m.r. spectrum almost identical to that of isopropyl α -D-glucopyranoside tetraacetate, and the crude product readily yielded the latter crystalline from ethanol. Benzoylation provided a product with the n.m.r. spectrum shown in Fig. 57. The isopropyl signal pattern contained four distinct peaks composed of two doublets, spacing 6 c.p.s. at 8.75τ and 8.95τ . Only benzoylation at the 2-position can be reasonably expected to have such a profound effect on the chemical shifts of the isopropyl group, since the other positions are too remote. Also mechanistically only the 2-position is expected to be involved in the reaction. Furthermore, the n.m.r. spectrum of the product (Fig. 56) closely resembles that (Fig. 63) of the product obtained on reaction of 1,2-anhydro- α -D-glucose triacetate with isopropanol. Chromatography of the reaction products on DMSO impregnated paper confirmed the presence of a free hydroxyl group

in the products, since the compounds virtually did not move at all.

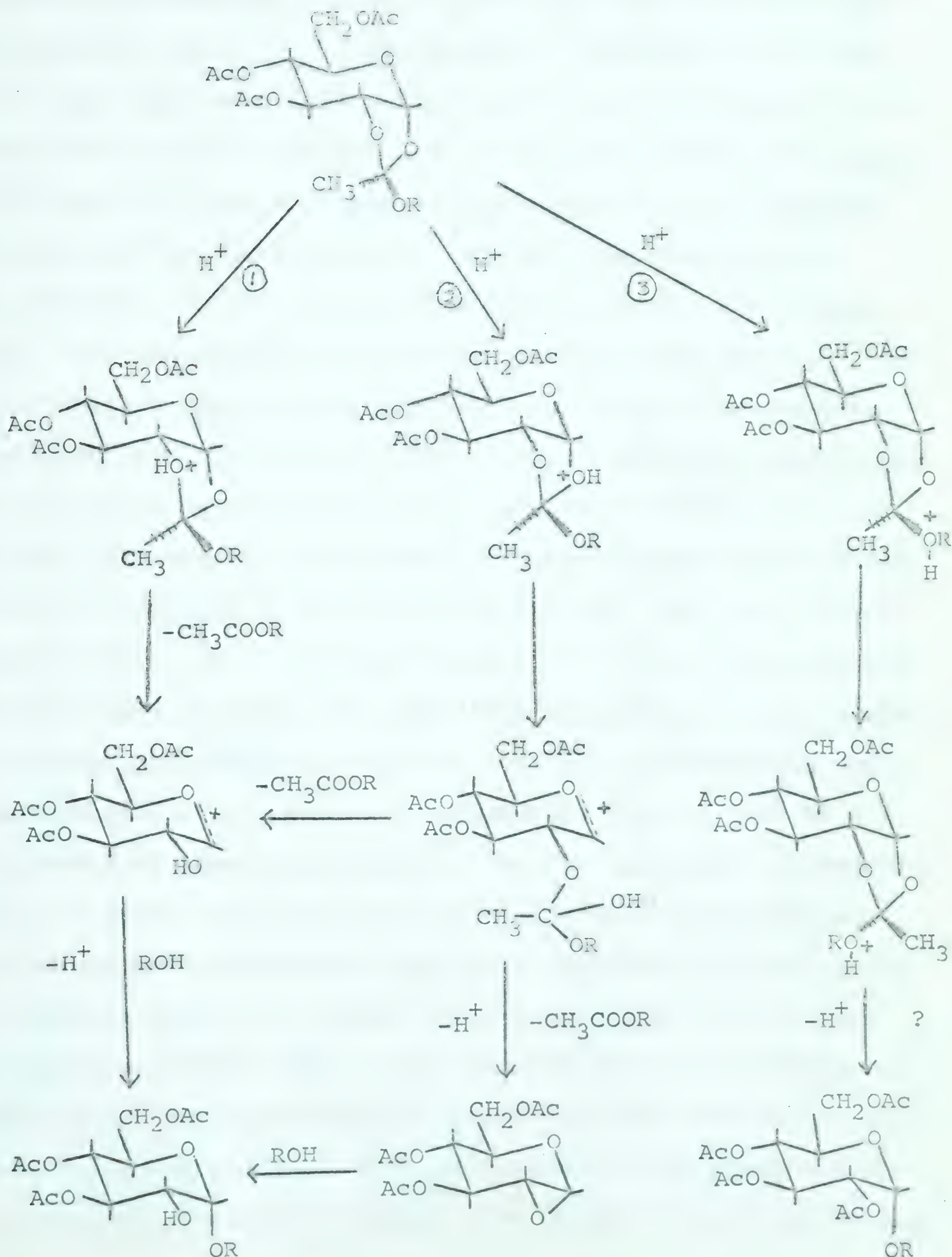
When 13 moles of isopropanol were used per mole of the isopropyl orthoacetate (35) in methylene chloride and with p-toluenesulphonic acid as the catalyst, the analysis of the products by g.-l.p.c. by the standard method (Table IV) showed that there was no significant difference in the yield of the products from the case when only one mole of the alcohol was used per mole of orthoester.

In the reaction of the t-butyl orthoacetate (36) under the standard conditions, it was found that the volatile components of the reaction contained isobutylene and t-butyl acetate as well as unreacted t-butanol. It was therefore obvious that p-toluenesulphonic acid is too strong an acid to be used with tertiary alcohols which readily dehydrate. The water liberated may be expected to give rise to transient acid orthoesters which will decompose to products which will analyse as glucose with the analytical procedure used. Nevertheless when a weaker acid such as picric acid was used, good yields of the α -glucoside may be obtained as already seen.

Scheme VI for the mechanism of the reaction of orthoesters with alcohols in the presence of acid catalysts seems the most reasonable. Routes (1) and (2) lead essentially to the same product. The cyclic carbonium ions stabilized by the pyranose ring oxygen are similar to intermediates postulated in the anomerization of β -glucosides with strong Lewis acids (40), although Lindberg (39) believes that the pyranose ring is opened. At any rate since the α -anomer is thermodynamically more stable, it is not

Scheme VI

Possible Mechanistic Routes for the Formation of α -Glucosides from α -D-Glucopyranose 1,2-Orthoacetates on Acid Catalysis



surprising that about 70% of the α -anomer is formed. Route (3) is known to occur from the formation of the equilibrium mixture of the diastereoisomers in acid solution, as determined from the n.m.r. spectrum (Fig. 65) of the product resulting on the treatment of pure "exo"-isopropyl orthoacetate (35) in methylene chloride containing picric acid and a trace of isopropanol. The signals at 8.31τ and 8.47τ may be compared with those at 8.29τ and 8.45τ when chloroform is the solvent in Fig. 39. The last stage in route (3) which involves the genuine rearrangement of the orthoacetate, the possibility of which led to the investigation of the orthoacetates as intermediates in the formation of α -glucosides, has not been shown to occur. There is some indication that it may occur to a small extent. For example when orthoacetates are reacted with approximately equimolar p-toluenesulphonic acid in the absence of an alcohol a syrup was obtained with the n.m.r. spectrum shown in Fig. 63. The rough triplet at 8.8τ may be attributed to the isopropyl grouping of a glucoside present as a minor component, although the concentration must have been sufficiently small to escape detection of isopropyl D-glucoside tetraacetate on a DMSO impregnated paper chromatogram. On the other hand a reaction under the standard conditions of 0.2 of a mole of the acid per mole of isopropyl orthoacetate (35), but omitting the alcohol led to an analysis under the standard procedure of 20% of isopropyl α -D-glucoside, 4.6% of the β -anomer and 27% of glucose. The n.m.r. spectrum of the reaction solution just before the isolation of the products had a sharp signal at 8.27τ (external TMS) which was lying on an ill-defined broad signal. The signal at 8.27τ is without

doubt that of the unreacted orthoacetate and, whilst because of the presence of the ill-defined signal no accurate calculation of the amount of unreacted orthoester could be made, a value of around 30% is indicated, and this would account for the high proportion of glucose in the analysis.

Apart from the small amounts of isopropyl glucoside formed, the main course of the reaction must result in oligo- and poly-saccharide formation, as indicated firstly from paper chromatograms which contain bands at the origin of very slow moving material. This is confirmed by the n.m.r. spectrum in Fig. 64. The extremely bad resolution is expected of oligo- and poly-saccharides. The strong resemblance of Fig. 64 to Fig. 61 is noteworthy. Fig. 61 is the n.m.r. spectrum of the product obtained from the reaction of "Brigl's Anhydride" with 2/5 of a molar amount of p-toluenesulphonic acid. "Brigl's Anhydride" is known to polymerize on heat to give oligo-saccharides (113), and the 1,2-linked sugar, kojibiose was one of the isolated products. The acid catalysed polymerization of "Brigl's Anhydride" may be expected to give mainly 1,2-linked polysaccharides if it first reacts to give the intermediate X shown in Scheme VI. The n.m.r. spectrum, Fig. 61, is not inconsistent with such a product. If the intensity of the acetyl groups corresponds to 9 protons, then in the range 5.5-6.7 τ there are about 4 protons and from 4.1-5.5 τ there are 3 protons. The proton on carbon-2 since it is not deshielded by an acetyl group would be expected to be to higher field than protons on carbon-1, -3 and -4 and hence have a chemical shift of approximately that of carbon-5 and -6 protons. Therefore the intensities in Fig. 61

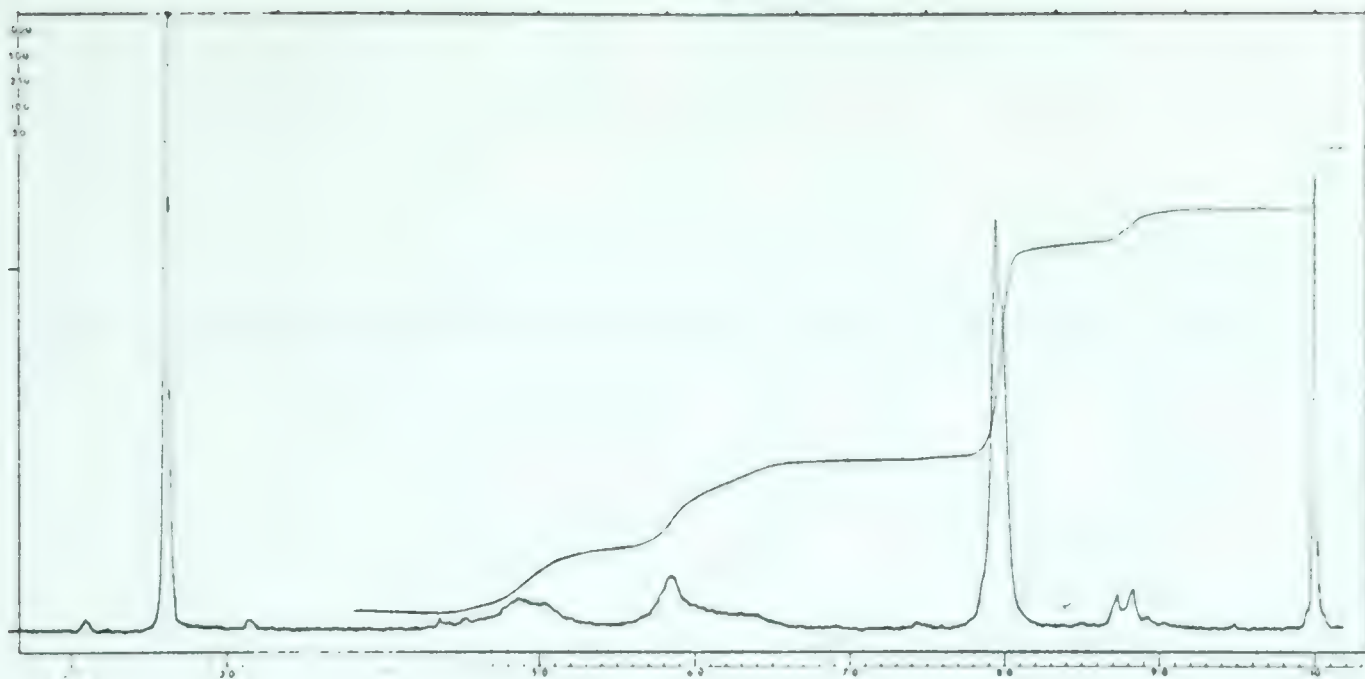


Fig. 58. The Product from the Reaction of Triethyloxonium Fluoroborate and α -D-Glucopyranose 1,2-(Isopropyl Orthoacetate)-3,4,6-triacetate, Experimental E.1.d.(i). (Chloroform).

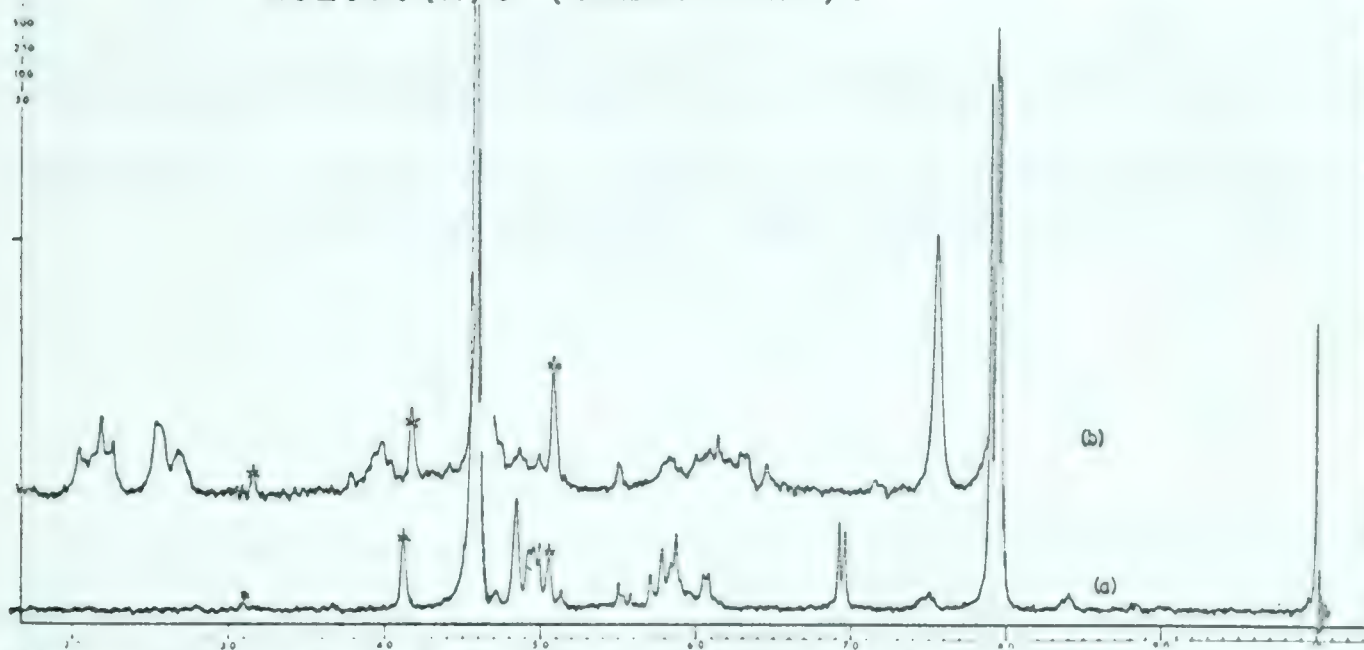


Fig. 60. (a) 3,4,6-Tri-O-acetyl-1,2-anhydro- α -D-glucopyranose ("Brigl's Anhydride"), (b) After adding one Mole-equivalent of p-Toluenesulphonic Acid. (The Region of 7τ was scanned within one minute) (Methylene Chloride).

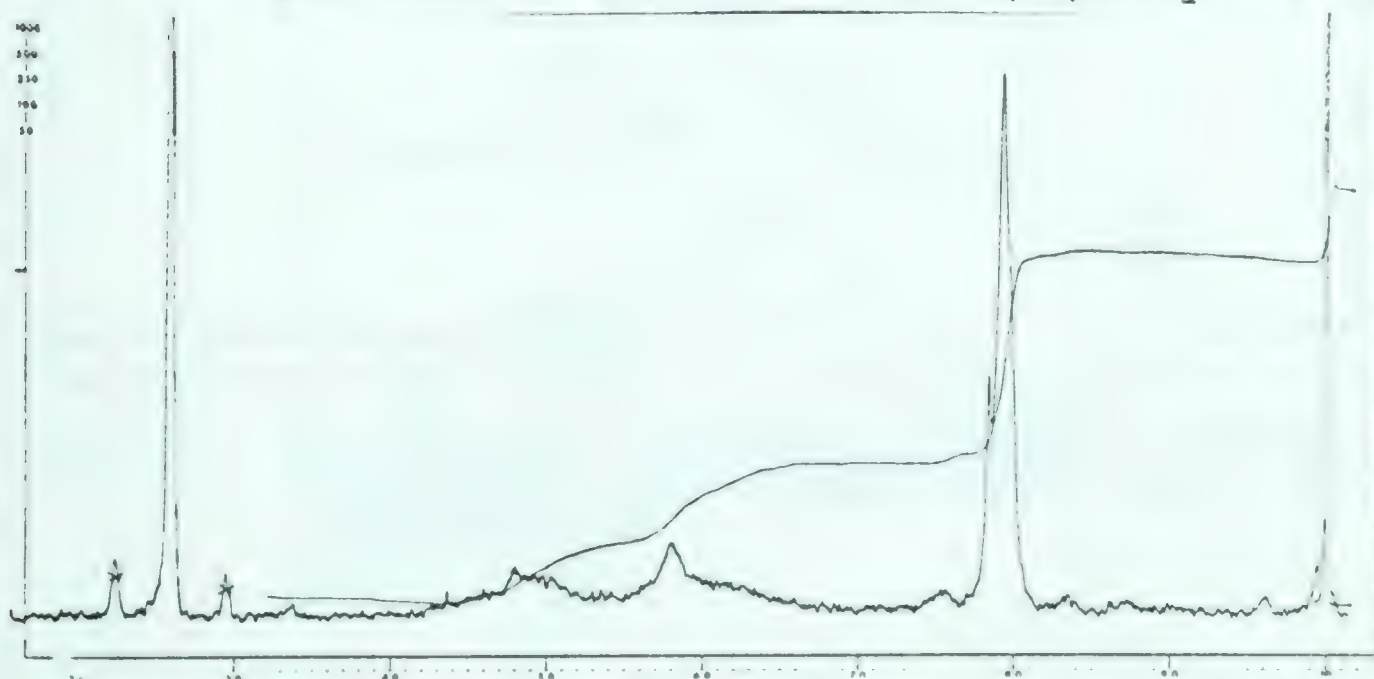


Fig. 61. The Product of the Reaction of "Brigl's Anhydride" with p-Toluenesulphonic Acid, Experimental B.2.b. (Chloroform).

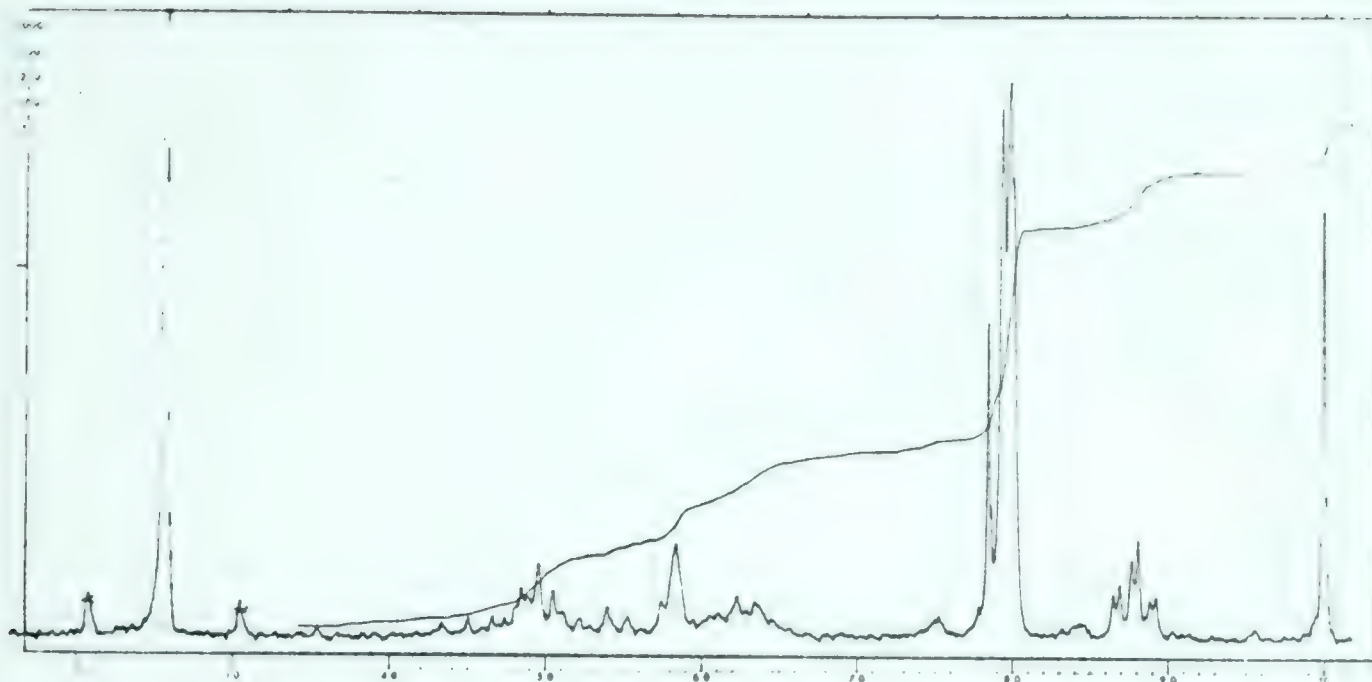


Fig. 62. A Mixture of Ethyl 2,3,4,6-Tetra-O-acetyl- α - and β -D-glucopyranosides, Experimental E.2.c. (i). (Chloroform).

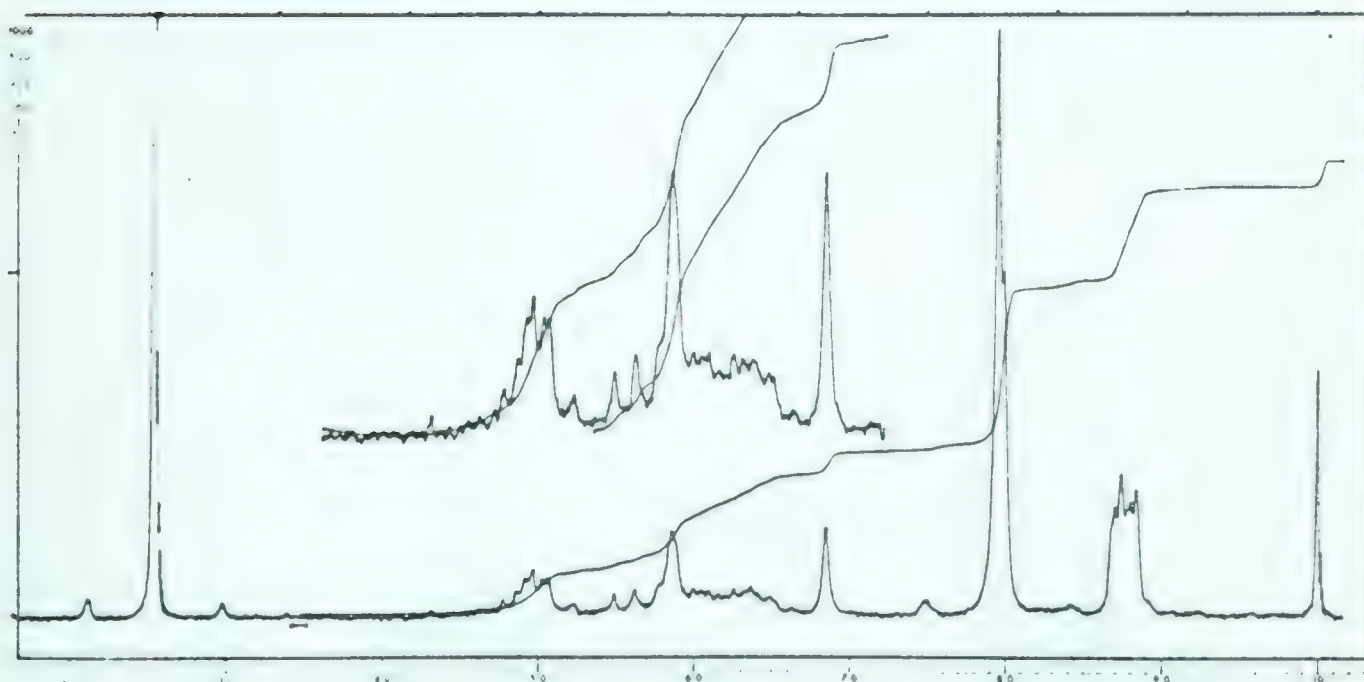


Fig. 63. A Mixture of Isopropyl 3,4,6-Tri-O-acetyl- α - and β -D-glucopyranosides, Experimental E.2.c.(ii). (Chloroform).

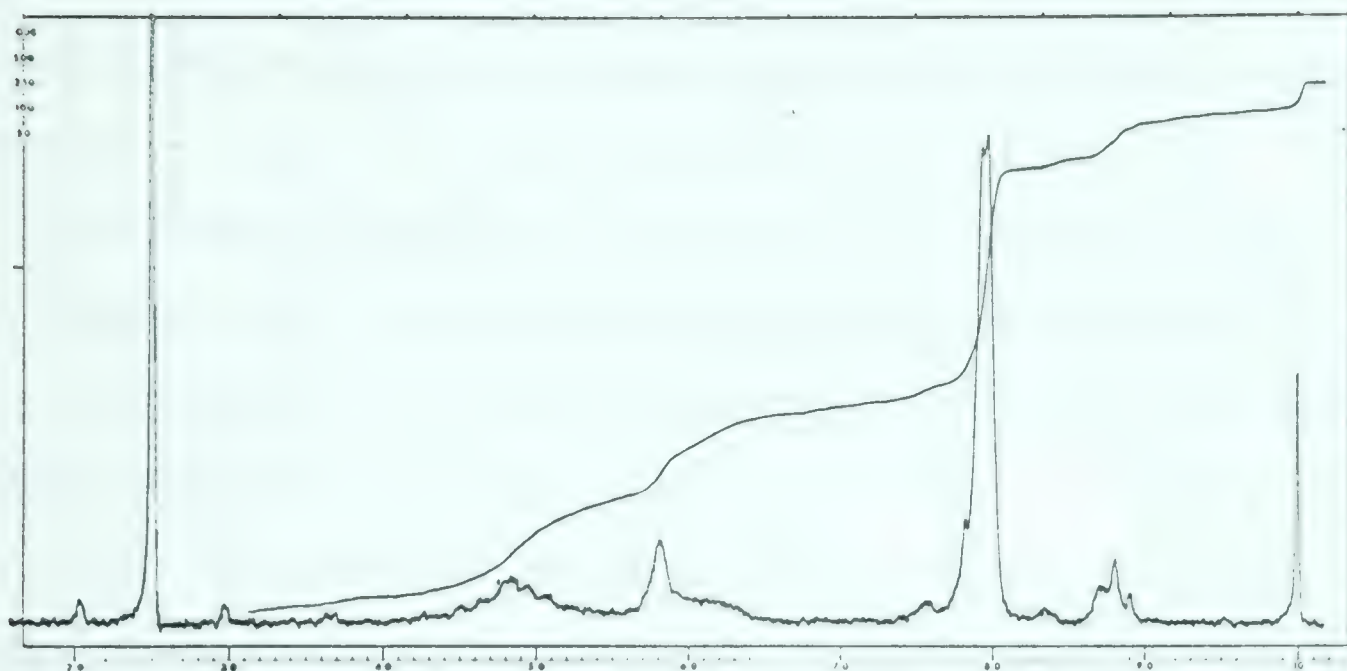


Fig. 64. The Product of the Reaction of α -D-Glucopyranose 1,2-(Isopropyl Orthoacetate)-3,4,6-triacetate (35) with p-Toluenesulphonic Acid after Reacetylation, Experimental E.2.d. (Chloroform).

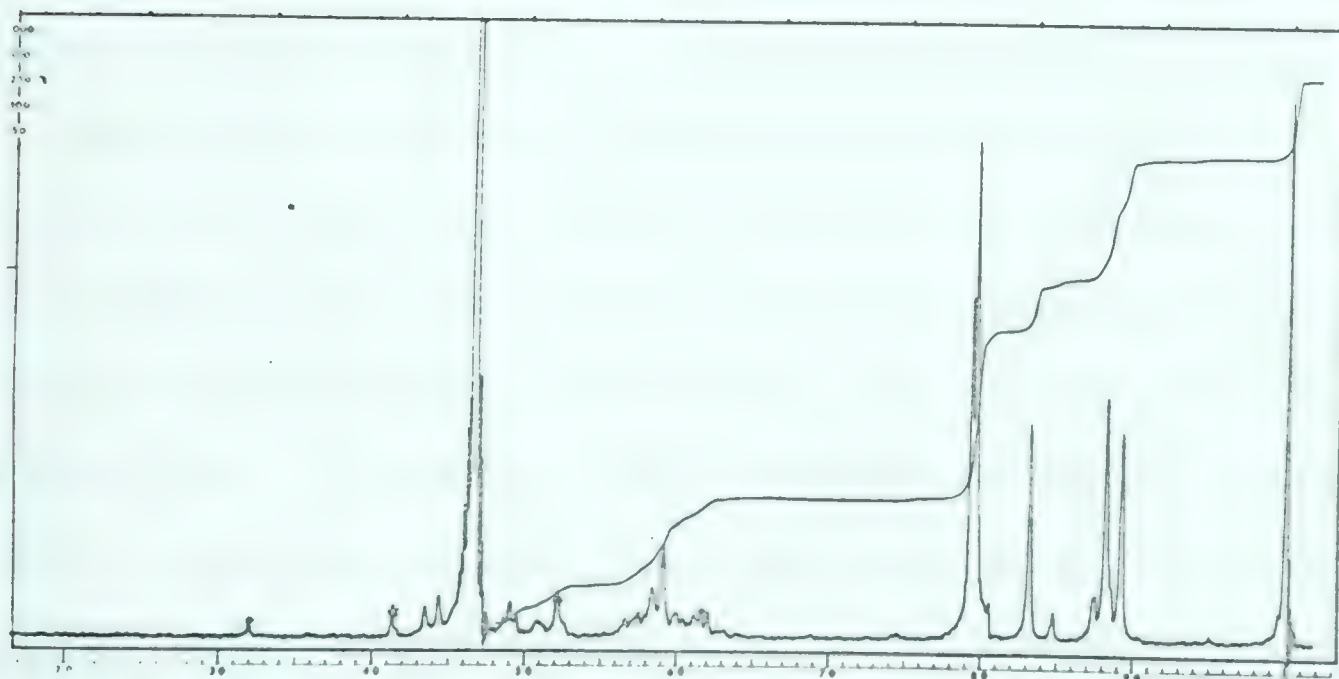


Fig. 65. The Product Obtained on Treatment of Pure "Exo" α -D-Glucopyranose 1,2-(Isopropyl Orthoacetate)-3,4,6-triacetate with Picric Acid, Experimental D.2.f. (Methylene Chloride).

correspond to a 1,2-linked polysaccharide although it must be pointed out that any combination of 1,2-, 2,2- and 1,1-linked polysaccharides will give the same general structure in their n.m.r. spectra.

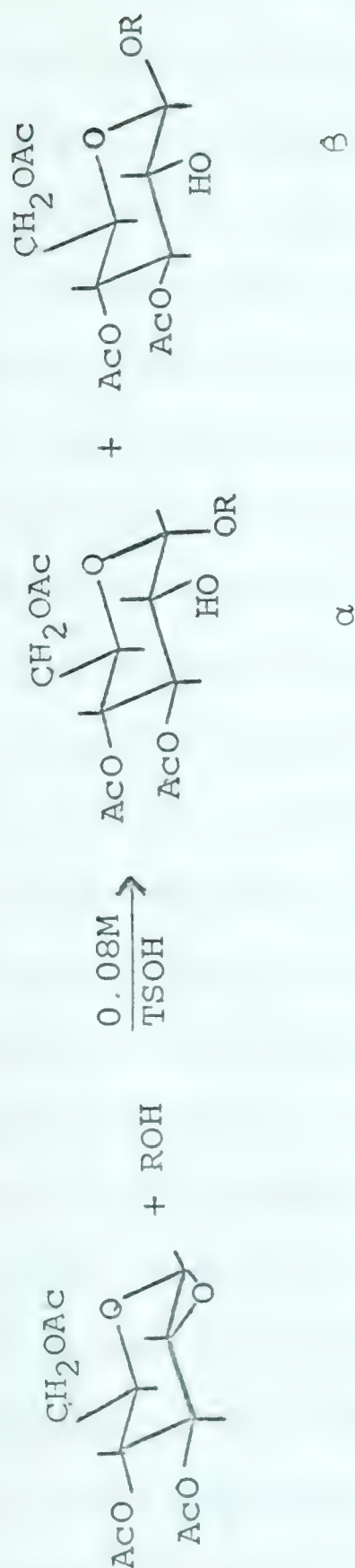
In view of the close similarity between Figs. 61 and 64 and in view of the intermediate X postulated in Scheme VI, it was of interest to see if it were possible to actually isolate "Brigl's Anhydride" from a reaction of the orthoesters with p-toluenesulphonic acid. In order to do so it must be possible to isolate "Brigl's Anhydride" back again when it is itself treated under the reaction conditions used. However when "Brigl's Anhydride" was treated with a 0.2 molar amount of p-toluenesulphonic acid five times, rapid rises in rotation were observed of equal value, except for the last addition, by when nearly a mole of the acid had been added per mole of the anhydride. In an experiment where one mole of acid was added to one mole of "Brigl's Anhydride", the characteristic doublet in the n.m.r. spectrum of the anhydride at 6.95τ , spacing 2 c.p.s., (Fig. 60), assigned to the 2-proton, had disappeared within a minute. Thus the p-toluenesulphonic acid must actually react with the anhydride, probably to give the unstable 1-O-tosylate. Although no well defined anomeric proton signal could be observed in the n.m.r. spectrum (Fig. 60) a rough signal at 3.98τ could be attributed to a 1-O-tosylate. Thus in the experiment when successive amounts of the acid were added, the first addition corresponded to the immediate reaction of 1/5 of the anhydride. If it is assumed that a tosylate was formed and had not time to decompose significantly, an approximate value for its

specific rotation may be calculated as $[\alpha]_D + 150^\circ$ in methylene chloride, which strongly suggests the α -anomer. This would require a cis-opening of the epoxide ring whereas normally epoxide rings are opened with Walden inversion at one of the carbon atoms forming the ring (114). This consumption of the acid explains why in the reaction of orthoesters if trace amounts of acids are added the initial rapid rise in rotation tails off but is observed to increase on further addition of acid. Also in the experiments with picric acid as the catalyst (Experimental E.1.c.(ii)), when the syrup was purified by passing it down an alumina column, the colorless eluate turned yellow as it was evaporated. Thus a labile compound containing picric acid is indicated, possibly the 1-O-picrate since picric acid will be expected to compete with the alcohol as the nucleophile.

In spite of the fact that "Brigl's Anhydride" obviously cannot be isolated under the reaction conditions it was interesting to determine if it was a transient intermediate. In order to test this, "Brigl's Anhydride" was substituted for the orthoester under the standard reaction conditions. The analysis of the products of the reaction by the usual procedure is shown in Table V, for the two cases when ethanol and isopropanol are the alcohols. The predominant glucoside now formed is the β -anomer. The n.m.r. spectrum of the direct product of the reaction when isopropanol was the alcohol is shown in Fig. 63 and the similarities with Fig. 56 are obvious, even though a much greater yield of the α -glucoside was obtained from the orthoacetate reaction. This confirms the evidence that the product of the orthoester reaction contains

TABLE V

yields of α - and β -Glucoside Formation from 3,4,6-Tri-O-acetyl-1,2-anhydro- α -D-Glucopyranose



Ratio of α - and β -Glucosides Formed

R

α β

40.8 59.2

41 59

42.5 57.5

Ethyl

Isopropyl

See Experimental E.2.c.(i) and (ii).

a free 2-hydroxyl group. The direct products could be acetylated to give n.m.r. spectra (e.g. Fig. 62) closely corresponding to the mixture of alkyl α - and β -D-glucopyranoside tetraacetates. About 13% of the "Brigl's Anhydride" reacts to give oligo- and poly-saccharides, as calculated from the relative intensities of the alkyl and acetate signals in the n.m.r. spectra. This was confirmed by an examination of the paper chromatograms of the deacetylated products. Both when ethanol or isopropanol were used as the alcohols, the bands on the paper chromatogram at R_G values of 0.079, 0.296 and 0.59 correspond to oligo- or poly-saccharides.

The above observation that "Brigl's Anhydride" reacts to give mainly β -glucosides under the standard conditions, indicates that if it is an intermediate in the orthoester reaction, only a small fraction of the reactions proceeds by this route. Thus, the postulated intermediate X probably does not form to an appreciable extent when "Brigl's Anhydride" reacts with alcohols under acidic conditions. Instead, the reaction must proceed mainly by way of an α -1-O-tosylate or the protonated epoxide ring with Walden inversion at the anomeric center. The yield of the α -anomer was significant and it may arise from an intermediate such as X.

That the reaction conditions used in the acid-catalysed alcoholyses of the orthoesters did not cause anomerization of the first-formed β -glucosides is evident since isopropyl β -D-glucopyranoside tetraacetate did not mutarotate under the reaction conditions and could be isolated again. It is extremely unlikely that if the 2-position contained a free hydroxyl group instead of being acetylated that it would mutarotate. Also the yields of

alkyl 3,4,6-tri-O-acetyl- β -D-glucopyranosides were much higher starting from "Brigl's Anhydride" than from the orthoacetates.

The reaction of the dimethyl orthocarbonate (49) under the standard reaction conditions but without the addition of an alcohol, as may be expected in the light of the further elucidation of the reactions of orthoesters under acidic conditions, gave rise to very little methyl glucoside formation if any. The volatile component at 6.18τ in the n.m.r. spectrum of the reaction mixture is almost certainly dimethyl carbonate. Since the starting material was not pure dimethyl orthocarbonate (49), the methoxy signals of low intensity at 6.43τ and 6.53τ assigned to α - and β -methyl glucosides and the methoxy-carbonyl group at 6.17τ are probably due to the impurities that were present in the reactant.

It was found that when triethyloxonium fluoroborate (75) was used as the catalyst in an attempt to form α -glucosides from orthoesters, a small amount of a disaccharide was isolated crystalline. Its high rotation of $[\alpha]_D + 228^\circ$ in chloroform indicated an α,α -linked disaccharide. The n.m.r. spectrum (Fig. 59) taken with an HR 100 Varian spectrometer together with double irradiation experiments proved the structure to be hexa-O-acetyl-1',2-anhydro [2'-(α -D-glucopyranosyl)] α -D-glucopyranose. Because of the symmetry of such a structure, the protons in one pyranose ring will have identical chemical shifts with those in the other ring. The triplet at 4.60τ , spacing 9.5 c.p.s. is readily assigned to the 3-proton, coupled diaxially to the 2- and 4-protons. It is relatively strongly deshielded compared to the other protons because of the 1,3-diaxial relationship with the anomeric oxygen. At 4.98τ ,

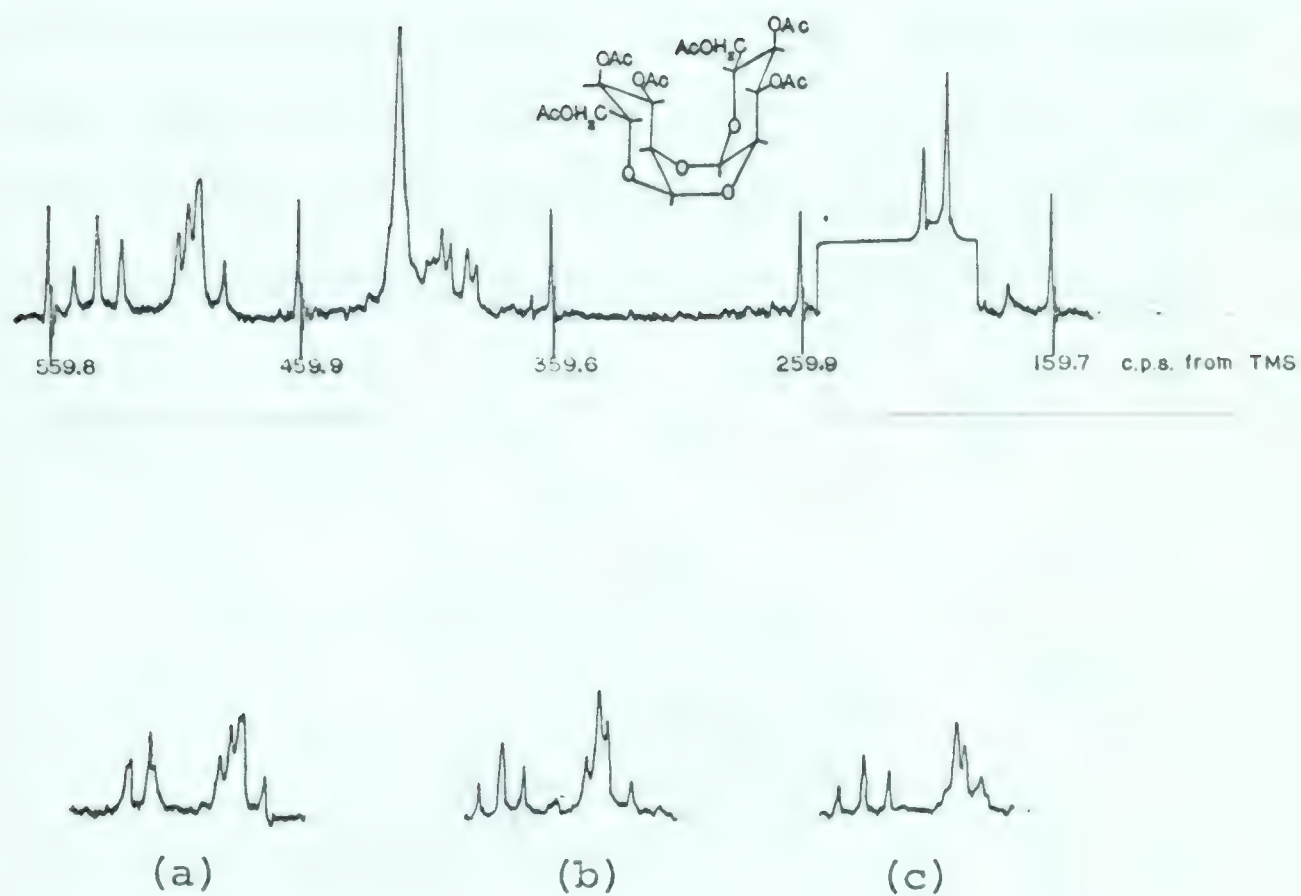
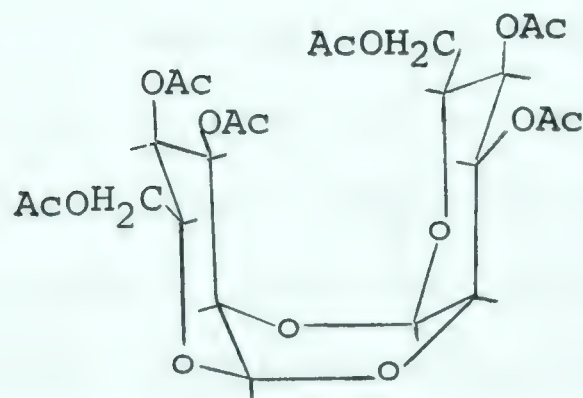


Fig. 59. Hexa-O-acetyl-1',2-anhydro-[2'-(α -D-glucopyranosyl)] α -D-Glucopyranose (100 Mc.p.s.), Discussion p. 161 for Details of Decoupling (Chloroform). (Acetyl signals at reduced amplitude).

spacing 3 c.p.s., and at 5.01τ , spacing 9 c.p.s., are the anomeric and 4-protons respectively. The two 6-protons and the 5-proton occur in the expected region of about $5.8-6\tau$ but are not well resolved. The 2-proton is found at 6.03τ as a quartet. Since the 3- and 4-protons are chemically well shifted it is safe to assume (115) spacings can be equated with the coupling constants, i.e. 3 c.p.s. coupling with the anomeric proton and 9.5 c.p.s. with the 3-proton. The acetyl groups are found at 7.90τ , intensity corresponding to one group, and 7.99τ , intensity corresponding to two groups. That the acetyl group at 7.90τ is relatively well deshielded may be due to the probable boat conformation of the 1,4-dioxane ring which connects the pyranose rings (Diag. 5).



Diag. 5.

It is seen that the 3-O-acetyl groups are in a relatively congested area of the molecule. All the assignments made were confirmed by the double irradiation experiments. Thus a side band 143 c.p.s. upfield from the 3-proton caused the latter to collapse from a triplet to a doublet (Fig. 59a). The weak splitting of the two peaks of the doublet are considered to be due to long range coupling. Similarly a side band 111 c.p.s. upfield from the anomeric proton resulted in its collapse to a singlet (Fig. 59b). Finally, a side band at 42 c.p.s. downfield from the 4-proton caused it to form an ill-defined doublet (Fig. 59c), on which the anomeric signal was superimposed as a doublet. The structure of the disaccharide is thus in no doubt. However, it only comprised a small fraction of the product of the reaction. The major product was shown on deacetylation and paper chromatography to consist of material with an R_G value of 0.22, and it is thus probably a disaccharide. Since it was non-reducing (the silver nitrate spray reagent did not reveal any band), it is most likely a diastereoisomer of the above anhydrodisaccharide. It was not further characterized, but is probably the α,β -linked isomer. When hydrogen fluoroborate was prepared by adding isopropanol to the triethyloxonium fluoroborate salt in methylene chloride to ensure the presence of a proton donor, essentially the same course of reaction was obtained, as determined by a comparison of the n.m.r. spectra of the crude reaction product (Fig. 58) and of the paper chromatograms of the deacetylated product.

The reactions of orthoesters alone or with alcohols in the presence of acid catalysts are obviously potentially of great sig-

nificance, principally with regard to the formation of α -glucosides but also for the preparation of new disaccharides or oligosaccharides. It appears that many new fields of research have been opened up, all both exciting theoretically and mechanistically, and also from a practical viewpoint. Without the aid of modern physical tools and in particular n.m.r. spectrometers, progress in this field would be very slow.

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